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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02021861.6

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
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Azole[1,2-C]quinazoline derivatives

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AZOLE [1,2-C]QUINAZOLINE DERIVATIVES

DETAILED DESCRIPTION OF INVENTION

TECHNICAL FIELD

The present invention relates to novel azole[1,2-c]quinazoline derivatives, processes for preparing them and pharmaceutical preparations containing them. The azole-[1,2-c]quinazoline derivatives of the present invention exhibit enhanced potency for phosphotidylinositol-3-kinase-γ (PI3K-γ) inhibition and can be used for the prophylaxis and treatment of diseases associated with PI3K-γ activity.

More specifically, the azole[1,2-c]quinazoline derivatives of the present invention are useful for treatment and prophylaxis of diseases as follows: inflammatory and immunoregulatory disorders, such as asthma, atopic dermatitis, rhinitis, allergic rhinitis, allergic diseases, COPD, septic shock, arthritis, joint diseases and myocardial injuries, as well as autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis.

The compounds of the present invention are also useful for treatment of ischemia, myocardial injury, pulmonary hypertension, renal failure, Huntington's chorea and cardiac hypertrophy, as well as neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease and focal ischemia, since the diseases also relate to PI3K-γ.

BACKGROUND ART

Signal transduction pathways originating from chemoattractant receptors are considered to be important targets in controlling leukocyte motility in inflammatory diseases. Leukocyte trafficking is controlled by chemoattractant factors that activate

heterotrimeric G-protein coupled receptors (GPCRs) and thereby trigger a complex variety of downstream intracellular events. Signal transduction at one of the pathways, ultimately resulting in mobilization of intracellular free Ca^{2+}, cytoskeletal reorganisation, and directional movement depends on lipid-derived second messengers produced by phosphoinositide 3-kinase (PI3K) activity [1,2].

PI3k phosphorylate the D3-hydroxyl position of the membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P_2) to yield phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P_3). Based on substrate specificity and protein structure, the PI3K family comprises three classes [3-5]. Of particular interest in leukocyte migration are class I PI3Ks, which are all involved in receptor-induced inflammatory cellular responses and are further divided into the subclasses IA (p110α, β, δ) and IB (p110γ). Class IA enzymes (p110α, β, δ) associate with a p85 adapter subunit, which contains two SH2 domains, to form a heterodimeric complex. This complex is able to recognize phosphotyrosine YxxM motifs, resulting in association with receptor tyrosine kinases and subsequent activation of the enzyme through receptor tyrosine kinases [1,2]. In contrast, the class IB (p110γ) enzyme, whose expression is largely confined to leukocytes, is activated by the G protein βγ complex, and functions downstream of seven transmembrane chemoattractant receptors [6-8]. The p101 adapter protein, which bears no resemblance to any other known protein, is essential for the Gβγ responsiveness of the PI3Kγ. [9-11].

Recent studies in mice lacking functional PI3Kγ (PI3Kγ-/- mice), which were viable, fertile, and displayed a normal life span in a conventional mouse facility, have revealed that neutrophils are unable to produce PtdIns(3,4,5)P_3 when stimulated with GPCR agonists such as fMLP, C5a or IL-8. This demonstrates that PI3Kγ is the sole PI3K that is coupled to these GPCRs in these cells [12-15]. Moreover, PtdIns(3,4,5)P_3-dependent activation of protein kinase B (PKB) was also absent in those neutrophils, while PKB could still be activated by GM-CSF or IgG/C3b-coated zymosan via either p110α, β or δ. At the same time, G-protein-mediated responses such as PLCβ activation were intact. PI3Kγ-/- mice showed impaired thymocyte

development and increases in neutrophil, monocyte, and eosinophil populations [13]. Furthermore, neutrophils and macrophages isolated from PI3Kγ-/- mice exhibited severe defects in migration and respiratory burst in response to GPCR agonists and chemotactic agents [13,15]. Expression of PI3Kγ was also examined in transgenic mice expressing green fluorescence protein (GFP) under the control of the endogenous PI3Kγ promoter. GFP was detected in spleen and bone marrow cells, and neutrophils, suggesting that the expression of PI3Kγ is restricted to hematopoietic cells [14]. Collectively, the class IB phosphoinositide 3-kinase PI3Kγ seems to be pivotal in the control of leukocyte trafficking and accordingly the development of isotype-selective inhibitors of PI3Kγ should be an attractive anti-inflammatory strategy.

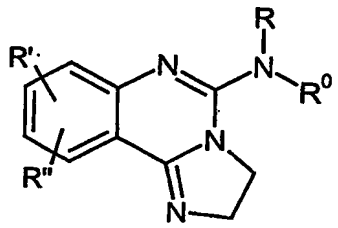
A specific inhibitor of PI3Kγ, which is expected to block signaltranduction from GPCR and the activation of various immune cells, should have a broad anti-inflammatory profile with potential for the treatment of inflammatory and immuno-regulatory disorders and diseases, including asthma, rhinitis, allergic diseases, septic shock, joint diseases and myocardial injuries, as well as autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis.

While no isotype-selective inhibitors of PI3Kγ has been reported yet, some PI3-kinase inhibitors has been identified: wortmannin, originally isolated as a fungal toxin from *Penicillium wortmannii* [16-18], the closely related but less well characterized demethoxyviridin [18],and LY294002, a morpholino derivative of the broad-spectrum kinase inhibitor quercetin [19].

Wortmannin and in particular LY294002 display little specificity and selectivity, as they also inhibit a variety of protein kinases related to PI3-kinases and show no preference within the PI3-kinase family [20]. Moreover, wortmannin inhibition is also observed for a number of unrelated protein kinases and phospholipase D. The lack of specificity and selectivity of both compounds, together with the instability

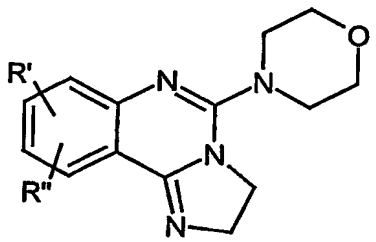
and irreversibility of wortmannin and the insolubility of LY294002, clearly limits their attractiveness as pharmaceutical agents..

US 3644354 discloses 5-substituted 2,3, dihydroimidazo[1,2-c]quinazolines represented by the general formula:



wherein R and R^0 is independently, hydrogen, lower alkyl, lower alkenyl; R' and R'' are independently, hydrogen, halogen, lower alkyl, lower alkoxy

or



as a hypotensive agents and coronary dilators

However, none of the references and other reference discloses azole[1,2-c]quinazoline derivatives having acylated amine or $-CR^5R^6-C(O)-$ ($R^5$is hydrogen or C_{1-6} alkyl and R^6 is halogen, hydrogen, or C_{1-6} alkyl) linker at the 5 position of azole[1,2-c]quinazoline and also azole[1,2-c]quinazoline derivatives having PI3K-γ inhibitory activity.

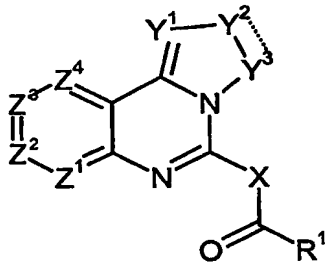
The development of a compound, having effective anti-inflammatory actions based on a specific and selective inhibitory activity to PI3K-γ and can be used for the

prophylaxis and treatment of diseases associated with PI3K-γ activity has been still desired.

SUMMARY OF THE INVENTION

As a result of extensive studies on chemical modification of azole[1,2-c]quinazoline derivatives, the present inventors have found that the compounds of novel chemical structure related to the present invention have unexpectedly excellent PI3K-γ inhibitory activity. The present invention has been accomplished based on these findings.

This invention is to provide novel azole[1,2-c]quinazoline derivatives of the formula (I) their tautomeric and stereoisomeric forms, and salts thereof.



wherein

X is NH, or CR^5R^6;

Y^1 is N or CR^3;

Y^2 and Y^3 are independently selected from the group consisting of CH, nitogen, CR^3R^4, or NR^4; the chemical bond between Y^2----Y^3 is selected from the group consisting of a single bond and double bond, Y^2 and Y^3 are the same or different represent CH or nitrogen when the bond is a double, Y^2 and Y^3 are the same or different represent CR^3R^4 or NR^4 when the bond is a single;

Z^1, Z^2, Z^3 and Z^4 are the same or different represent N, CH, or CR^2;

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, C_{1-6} alkoxyaryl, aryloxy, or heteroaryl, C_{1-6} alkoxy optionally substituted by C_{1-6} alkyl, aryl, or one or more halogen, C_{1-6} alkylthio, N-arylamino, N(aryl C_{1-6}alkylene)amino, a 3 to 8 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of O, S, and N, and said ring is optionally having one or more substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, amino, C_{1-6}alkyl optionally substituted by one or more halogen, C_{3-8}cycloalkyl, C_{1-6}alkoxy, carboxy, C_{1-6} alkylthio, C_{1-6}alkylsulfonyl, sulfamoyl, N- C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, heteroaryl optionally substituted by C_{1-6} alkyl or C_{1-6}alkoxy, heteroarylamino, heteroarylcarbonyl, heterocyclyl, heterocyclylcarbonyl, N-(C_{1-6}alkanoyl)amino, N(carboxyC_{1-6}alkylene)N(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycabonyl)amino, and aryl C_{1-6}alkoxycarbonyl,

or

said a 3 to 8 membered saturated or unsaturated ring is optionally fused by a 5 to 8 membered unsaturated ring optionally interrupted by 0 to 3 heteroatoms selected from the group consisting of O, S, and N,

wherein said a fused ring is optionally substituted by C_{1-6}alkyl or one or more halogen substituted C_{1-6}alkyl;

R^2 is hydroxy, halogen, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by cyano, one or more halogen, or amino, N-C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, or heterocyclyl;

R^3 is hydrogen, halogen, C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy or one or more halogen, or carbamoyl;

R^4 is hydrogen or C_{1-6} alkyl;

R^5 is hydrogen or C_{1-6} alkyl; and

R^6 is halogen, hydrogen, or C_{1-6} alkyl.

The Alkyl per se and "alk" and "alkyl" in alkoxy, alkanoyl, alkylamino, alkylaminocarbonyl, alkylaminosulphonyl, alkylsulphonylamino, alkoxycarbonyl, alkoxycarbonylamino and alkanoylamino represent a linear or branched alkyl radical having generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkanoyl illustratively and preferably represents acetyl and propanoyl.

Alkylamino represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-methyl-N-n-propylamino, N-isopropyl-N-n-propylamino, N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino and N-n-hexyl-N-methylamino.

Alkylaminocarbonyl or alkylcarbamoyl represents an alkylaminocarbonyl radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylaminocarbonyl, ethylaminocarbonyl, n-propylamino-

carbonyl, isopropylamino-carbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-diethylaminocarbonyl, N-ethyl-N-methylaminocarbonyl, N-methyl-N-n-propylaminocarbonyl, N-isopropyl-N-n-propylaminocarbonyl, N-t-butyl-N-methylaminocarbonyl, N-ethyl-N-n-pentylamino-carbonyl and N-n-hexyl-N-methylaminocarbonyl.

Alkylaminosulphonyl represents an alkylaminosulphonyl radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylaminosulphonyl, ethylaminosulphonyl, n-propylaminosulphonyl, isopropylaminosulphonyl, tert-butylaminosulphonyl, n-pentylaminosulphonyl, n-hexyl-aminosulphonyl, N,N-dimethylaminosulphonyl, N,N-diethylaminosulphonyl, N-ethyl-N-methylamino-sulphonyl, N-methyl-N-n-propylaminosulphonyl, N-isopropyl-N-n-propylaminosulphonyl, N-t-butyl-N-methylaminosulphonyl, N-ethyl-N-n-pentylaminosulphonyl and N-n-hexyl-N-methylaminosulphonyl.

Alkylsulphonylamino illustratively and preferably represents methylsulphonylamino, ethylsulphonylamino, n-propylsulphonylamino, isopropylsulphonylamino, tert-butylsulphonylamino, n-pentylsulphonylamino and n-hexylsulphonylamino.

Alkoxycarbonyl illustratively and preferably represents methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl. Alkoxycarbonylamino illustratively and preferably represents methoxycarbonylamino, ethoxycarbonylamino, n-propoxycarbonylamino, isopropoxycarbonylamino, tert-butoxycarbonylamino, n-pentoxycarbonylamino and n-hexoxycarbonylamino.

Alkanoylamino illustratively and preferably represents acetylamino and ethylcarbonylamino.

Cycloalkyl per se and in cycloalkylamino and in cycloalkylcarbonyl represents a cycloalkyl group having generally 3 to 8 and preferably 5 to 7 carbon atoms,

illustratively and preferably representing cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Cycloalkylamino represents a cycloalkylamino radical having one or two (independently selected) cycloalkyl substituents, illustratively and preferably representing cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino and cycloheptylamino.

Cycloalkylcarbonyl illustratively and preferably represents cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl and cycloheptylcarbonyl.

Aryl per se and in arylamino and in arylcarbonyl represents a mono- to tricyclic aromatic carbocyclic radical having generally 6 to 14 carbon atoms, illustratively and preferably representing phenyl, naphthyl and phenanthrenyl.

Arylamino represents an arylamino radical having one or two (independently selected) aryl substituents, illustratively and preferably representing phenylamino, diphenylamino and naphthylamino.

Arylcarbonyl illustratively and preferably represents phenylcarbonyl and naphthylcarbonyl.

Heteroaryl per se and in heteroarylamino and heteroarylcarbonyl represents an aromatic mono- or bicyclic radical having generally 5 to 10 and preferably 5 or 6 ring atoms and up to 5 and preferably up to 4 hetero atoms selected from the group consisting of S, O and N, illustratively and preferably representing thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyridyl, pyrimidyl, pyridazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl.

Heteroarylamino represents an heteroarylamino radical having one or two (independently selected) heteroaryl substituents, illustratively and preferably representing thienylamino, furylamino, pyrrolylamino, thiazolylamino, oxazolylamino, imidazolyl-amino, pyridylamino, pyrimidylamino, pyridazinylamino, indolylamino, indazolylamino, benzofuranylamino, benzothiophenylamino, quinolinyl-amino, isoquinolinylamino.

Heteroarylcarbonyl illustratively and preferably represents thienylcarbonyl, furylcarbonyl, pyrrolylcarbonyl, thiazolylcarbonyl, oxazolylcarbonyl, imidazolylcarbonyl, pyridylcarbonyl, pyrimidylcarbonyl, pyridazinylcarbonyl, indolylcarbonyl, indazolylcarbonyl, benzofuranylcarbonyl, benzothiophenylcarbonyl, quinolinylcarbonyl, isoquinolinylcarbonyl.

Heterocyclyl per se and in heterocyclylcarbonyl represents a mono- or polycyclic, preferably mono- or bicyclic, nonaromatic heterocyclic radical having generally 4 to 10 and preferably 5 to 8 ring atoms and up to 3 and preferably up to 2 hetero atoms and/or hetero groups selected from the group consisting of N, O, S, SO and SO_2. The heterocyclyl radicals can be saturated or partially unsaturated. Preference is given to 5- to 8-membered monocyclic saturated heterocyclyl radicals having up to two hetero atoms selected from the group consisting of O, N and S, such as illustratively and preferably tetrahydrofuran-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, piperidinyl, morpholinyl, perhydroazepinyl.

Heterocyclylcarbonyl illustratively and preferably represents tetrahydrofuran-2-carbonyl, pyrrolidine-2-carbonyl, pyrrolidine-3-carbonyl, pyrrolinecarbonyl, piperidinecarbonyl, morpholinecarbonyl, perhydroazepinecarbonyl.

Halogen represents fluorine, chlorine, bromine and iodine.

This invention is also to provide a method for treating or preventing a disorder or disease associated with PI3K-γ activity in a human or animal subject, comprising

administering to said subject a therapeutically effective amount of the azole[1,2-c]quinazoline derivative shown in the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof.

Further this invention is to provide a use of the azole[1,2-c]quinazoline derivative shown in the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof in the preparation of a medicament. Preferably, said medicament is suitable for treating or preventing a disorder or disease associated with PI3K-γ activity.

The compounds of the present invention surprisingly show excellent PI3K-γ activity. They are, therefore, suitable for the production of medicament or medical composition, which may be useful to treat PI3K-γ related diseases.

More specifically, since the azole[1,2-c]quinazoline derivatives of the present invention inhibit PI3K-γ, they are useful for treatment and prophylaxis of diseases as follows:

Inflammatory and immunoregulatory disorders, such as asthma, atopic dermatitis, rhinitis, allergic rhinitis, allergic diseases, COPD, septic shock, arthritis, joint diseases and myocardial injuries, as well as autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis.

Therefore, PI3K-γ is an important target and inhibition of PI3K-γ is likely to be effective in the treatment of such inflammatory and immunoregulatory disorders and diseases.

The compounds of the present invention are also useful for treatment of ischemia, myocardial injury, pulmonary hypertension, renal failure, Huntington's chorea and cardiac hypertrophy, as well as neurodegenerative disorders such as Parkinson's

disease, Alzheimer's disease and focal ischemia, since the diseases also relate to PI3K-γ.

In one embodiment, the compounds of formula (I) are those wherein:

Z^1 and Z^3 are the same or different represent N or CH; and

Z^2 and Z^4 are the same or different represent CH or C R^2.

In another embodiment, the compounds of formula (I) are those wherein:

Z^1 and Z^3 are the same or different represent CH or C R^2;and

Z^2 and Z^4 are the same or different represent N or CH.

In another embodiment, the compounds of formula (I) are those wherein:

Z^1 and Z^4 are the same or different represent N or CH;

Z^2 and Z^3 are the same or different represent CH or CR^2;

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, methoxyphenyl, phenoxy, or thienyl, C_{1-6} alkoxy optionally substituted by C_{1-6} alkyl, phenyl, or one or more halogen, C_{1-6} alkylthio, N-phenylamino, N(phenyl C_{1-6}-alkylene)amino, a 3 to 8 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of O, S, and N, and said ring is optionally having one or more substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, amino, C_{1-6}alkyl optionally substituted by one or more halogen, C_{1-6}alkoxy, carboxy, C_{1-6} alkylthio, C_{1-6}alkylsulfonyl, sulfamoyl, N- C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6}-alkoxy, C_{1-6}alkoxycarbonyl, piperazinyl optionally substituted by C_{1-6} alkyl or

C_{1-6}alkoxy, N-(C_{1-6}alkanoyl)amino, N(carboxyC_{1-6} alkylene)N(C_{1-6}alkyl)-amino, N-(C_{1-6}alkoxycabonyl)amino, pyrrolyl, imidazolyl, pyrrolidinyl, pyridyl, and phenyl C_{1-6}alkoxycarbonyl,

or

said a 3 to 8 membered saturated or unsaturated ring is optionally fused by a 5 to 8 membered unsaturated ring optionally interrupted by 0 to 3 heteroatoms selected from the group consisting of O, S, and N,

wherein said a fused ring is optionally substituted by C_{1-6}alkyl or one or more halogen substituted C_{1-6}alkyl;

R^2 is hydroxy, halogen, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by cyano, one or more halogen, or amino, N-C_{1-6}-alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, or morpholinyl;

R^3 is halogen, hydrogen, C_{1-6} alkyl optionally substituted by aryl C_{1-6}alkoxy or one or more halogen, or carbamoyl;

R^4 is hydrogen or C_{1-6} alkyl;

R^5 is hydrogen or C_{1-6} alkyl; and

R^6 is hydrogen, halogen, or C_{1-6} alkyl.

In another embodiment, the compounds of formula (I) are those wherein:

Z^1 and Z^4 are the same or different represent CH or C R^2;

Z^2 and Z^3 are the same or different represent N or CH;

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, methoxyphenyl, phenoxy, or thienyl, C_{1-6} alkoxy optionally substituted by C_{1-6} alkyl, phenyl, or one or more halogen, C_{1-6} alkylthio, N-phenylamino, N(phenyl C_{1-6}alkylene)amino, a 3 to 8 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of O, S, and N, and said ring is optionally having one or more substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, amino, C_{1-6}alkyl optionally substituted by one or more halogen, C_{1-6}alkoxy, carboxy, C_{1-6} alkylthio, C_{1-6}alkylsulfonyl, sulfamoyl, N- C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, piperazinly optionally substituted by C_{1-6} alkyl or C_{1-6}alkoxy, N-(C_{1-6}alkanoyl)amino, N(carboxyC_{1-6} alkylene)N(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycabonyl)amino, pyrrolyl, imidazolyl, pyrrolidinyl, pyridyl, and phenyl C_{1-6}alkoxycarbonyl,

or

said a 3 to 8 membered saturated or unsaturated ring is optionally fused by a 5 to 8 membered unsaturated ring optionally interrupted by 0 to 3 heteroatoms selected from the group consisting of O, S, and N,

wherein said a fused ring is optionally substituted by C_{1-6}alkyl or one or more halogen substituted C_{1-6}alkyl;

R^2 is hydroxy, halogen, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by cyano, one or more halogen, or amino, N-C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, or morpholinyl;

R^3 is halogen, hydrogen, C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy, or one or more or carbamoyl;

R^4 is hydrogen or C_{1-6} alkyl;

R^5 is hydrogen or C_{1-6} alkyl; and

R^6 is hydrogen, halogen, or C_{1-6} alkyl.

In another embodiment, the compounds of formula (I) are those wherein:

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, methoxyphenyl, phenoxy, or thienyl, C_{1-6} alkoxy optionally substituted by C_{1-6} alkyl, phenyl, or mono, di, or tri, halogen, C_{1-6} alkylthio, N-phenylamino, N(phenyl C_{1-6}-alkylene)amino, a 3 to 8 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of O, S, and N, and said ring is optionally having one or more substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, amino, C_{1-6}alkyl optionally substituted by mono, di, or tri, halogen, C_{1-6}alkoxy, carboxy, C_{1-6} alkylthio, C_{1-6}alkylsulfonyl, sulfamoyl, N- C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6}-alkoxy, C_{1-6}alkoxycarbonyl, piperazinly optionally substituted by C_{1-6} alkyl or C_{1-6}alkoxy, N-(C_{1-6}alkanoyl)amino, N(carboxyC_{1-6} alkylene)N(C_{1-6}alkyl)-amino, N-(C_{1-6}alkoxycabonyl)amino, pyrrolyl, imidazolyl, pyrrolidinyl, pyridyl, and phenyl C_{1-6}alkoxycarbonyl,

or

said a 3 to 8 membered saturated or unsaturated ring is optionally fused by a 5 to 8 membered unsaturated ring optionally interrupted by 0 to 3 heteroatoms selected from the group consisting of O, S, and N,

wherein said a fused ring is optionally substituted by C_{1-6}alkyl or mono, di, or tri halogen substituted C_{1-6}alkyl;

R^2 is hydroxy, halogen, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by cyano mono, di or tri halogen, or amino, N-C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, or morpholinyl;

R^3 is halogen, hydrogen, C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy or one or more halogen, carbamoyl;

R^4 is hydrogen or C_{1-6} alkyl; and

R^5 is hydrogen or C_{1-6} alkyl; and

R^6 is halogen, hydrogen or C_{1-6} alkyl.

In another embodiment, the compounds of formula (I) are those wherein:

Z^1 and Z^4 are CH;

Z^2 and Z^3 are the same or different represent CH or C R^2;

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, methoxyphenyl, phenoxy, or thienyl, C_{1-6} alkoxy optionally substituted by C_{1-6} alkyl, phenyl, or mono, di, or tri, halogen, C_{1-6} alkylthio, N-phenylamino, N(phenyl C_{1-6}alkylene)amino, a 3 to 8 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of O, S, and N,

wherein siad ring is selected from the group consisting of cyclopropyl, cyclopentyl, cyclohexyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, piperidinyl, piperazinyl, pyrimidyl, furyl, pyrrolidinyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, and morpholinyl,

wherein said ring is optionally having 1 to 3 substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, amino, C_{1-6}-alkyl optionally substituted by mono, di or tri halogen, C_{1-6}alkoxy, carboxy, C_{1-6} alkylthio, C_{1-6}alkylsulfonyl, sulfamoyl, N-(C_{1-6}alkyl)-amino, di(C_{1-6})alkylamino, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, piperazinly optionally substituted by C_{1-6} alkyl or C_{1-6}alkoxy, N-(C_{1-6}alkylcabonyl)amino, N(carboxyC_{1-6} alkyl)N(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycabonyl)amino, imidazolyl, pyrrolyl, pyrrolidinyl, pyridyl, and phenyl C_{1-6}alkoxycabonyl,

or said a 3 to 8 membered saturated or unsaturated ring is optionally fused by a 5 to 8 membered unsaturated ring optionally interrupted by 0 to 3 heteroatoms selected from the group consisting of O, S, and N

wherein said fused ring is selected from the group consisting of benzothiophenly, benzimidazolyl, benzotriazolyl, benzothiazolyl, benzisothiazolyl indazolyl, quinolinly, and isoquinolinyl,

wherein said a fused ring is optionally substituted by C_{1-6}alkyl or mono, di, or tri halogen substituted C_{1-6}alkyl;

R^2 is chloro, bromo, fluoro, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by tri halogen, C_{1-6} alkoxy, or morpholinyl,

R^3 is halogen, hydrogen, C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy or one or more halogen, or carbamoyl;

R^4 is hydrogen, C_{1-6} alkyl or carbamoyl;

R^5 is hydrogen; and

R^6 is hydrogen.

In another embodiment, the compounds of formula (I) are those wherein:

X is NH;

Y^1 is N;

Y^2 and Y^3 are CR^3R^4;

Z^1 and Z^4 are CH;

Z^2 and Z^3 are the same or different represent CH or C R^2;

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, phenyl, C_{1-6}alkoxy substituted phenyl, phenoxy, or thienyl, cyclopropyl, cyclopentyl, cyclohexyl,

phenyl optionally substituted by halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, amino, N-(C_{1-6}alkyl cabonyl)amino, N-(C_{1-6}alkoxycabonyl)amino, di(C_{1-6})alkylamino, N-(carboxyC_{1-6}alkylene)N-C_{1-6}alkyl amino, C_{1-6}alkanoylamino, C_{1-6} alkylthio, C_{1-6}alkylsulfonyl, or sulfamoyl, piperazinyl optionally substituted by C_{1-6}alkyl, pyrrolyl, imidazolyl, or pyrrolidinyl, pyridyl optionally substituted by halogen,

hydroxy, C_{1-6}alkyl optionally substituted by one or more halogen, C_{1-6}alkoxy, C_{1-6} alkylthio, amino, di(C_{1-6})alkylamino, or C_{1-6}alkanoylamino,

pyrazinyl optionally substituted by C_{1-6} alkyl,

2-thienyl optionally substituted by halogen, nitro, cyano, or C_{1-6} alkyl,

3-thienyl optionally substituted nitro, pyrimidinyl, pyridazinyl, pyrrolyl optionally substituted by C_{1-6} alkyl,

piperidinyl optionally substituted by C_{1-6}alkoxycarbonyl, or benzyloxy-carbonyl,

piperazinyl, pyrimidyl, 2-furyl, 3-furyl, thienyl,

thiazolyl optionally substituted by C_{1-6}alkyl, pyridyl, or N-(C_{1-6}alkoxy-carbonyl)amino,

isothiazolyl, thiadiazolyl,

indolyl optionally substituted by C_{1-6}alkyl, benzimidazolyl optionally substituted by C_{1-6}alkyl optionally substituted by mono, di or tri halogen, benzotriazolyl optionally substituted by C_{1-6}alkyl, quinolyl benzthiazolyl, indole substituted by C_{1-6}alkyl, or bemzothhiophenyl

R^2 is hydroxy, halogen, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by cyano mono, di or tri halogen, or amino, N-C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, or morpholinyl;

R^3 is halogen, hydrogen, C_{1-6} alkyl or carbamoyl; and

R^4 is hydrogen or C_{1-6} alkyl.

In another embodiment, the compounds of formula (I) are those wherein:

X is CR^5R^6;

Y^1 is N;

Y^2 and Y^3 are $C\,R^3\,R^4$;

Z^1 and Z^4 are CH;

Z^2 and Z^3 are the same or different represent CH or $C\,R^2$;

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, substituted phenyl, or phenoxy, C_{1-6}alkoxy optionally substituted by phenyl, benzyl-amino, cyclopropyl, cyclohexyl, phenyl optionally substituted by chloro, hydroxy, nitro, cyano, carboxyl, C_{1-6} alkyl, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, amino, di(C_{1-6})alkylamino, C_{1-6}alkanoylamino, C_{1-6} alkylthio, C_{1-6}alkyl-sulfonyl, or sulfamoyl, pyridyl optionally substituted by halogen, C_{1-6}alkyl, C_{1-6}alkoxy, pyrazinyl optionally substituted by C_{1-6} alkyl, 2-thienyl optionally substituted by halogen, cyano or nitro, 3-thienyl optionally substituted by halogen, cyano or nitro, pyrimidinyl, pyridazinyl, pyrrolyl, piperidinyl piperazinyl, pyrimidyl, furyl, thiazolyl optionally substituted by C_{1-6}alkyl, cyano, or C_{1-6}alkoxycarbonylamino, pyridyl, thiadiazolyl, and indolyl optionally substituted by C_{1-6}alkyl, or benzothienyl; and

R^2 is chloro, bromo, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by tri-halogen, or C_{1-6} alkoxy;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is hydrogen; and

R^6 is hydrogen.

The preferable compounds of the present invention are as follows:

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-furamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophenecarboxamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3-thiophenecarboxamide,

3-amino-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,

4-amino-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,

4-(acetylamino)-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-1,2,3-benzotriazole-5-carboxamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3,4-dimethoxybenzamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-6-methylnicotinamide,

2-chloro-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,

6-chloro-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3-quinolinecarboxamide,

6-(acetylamino)-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,

N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,

N-(9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methyl-1H-benzimidazole-5-carboxamide,

N-(9-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,

N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,

N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-thiophenecarboxamide,
N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophenecarboxamide,
N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide,
N-(10-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophenecarboxamide,
N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophenecarboxamide,
N-(9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophenecarboxamide,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-pyrazinyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(4-pyridinyl)ethenol,
(1Z)-3,3,3-trichloro-1-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-propen-2-ol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-furyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-thienyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(1H-pyrrol-2-yl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-thienyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(1H-pyrrol-3-yl)ethenol,
(Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(1,3-thiazol-2-yl)ethenol,
(Z)-2-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethenol,
(Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-thienyl)ethenol,
N-{4-[(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyethenyl]phenyl}acetamide,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(6-methyl-3-pyridinyl)ethenol,
(Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(6-methyl-3-pyridinyl)ethenol,

and their tautomeric and stereoisomeric form, and salts thereof.

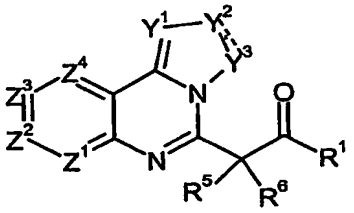
Further, the present invention provides a medicament which include one of the compounds described above and optionally pharmaceutically acceptable excipient.

EMBODIMENT OF INVENTION

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by reactions described below. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in "Protective Groups in Organic Synthesis (2nd Edition)" by Greene and Wuts.

The typical processes for preparing the compounds (I) of the present invention are explained below.

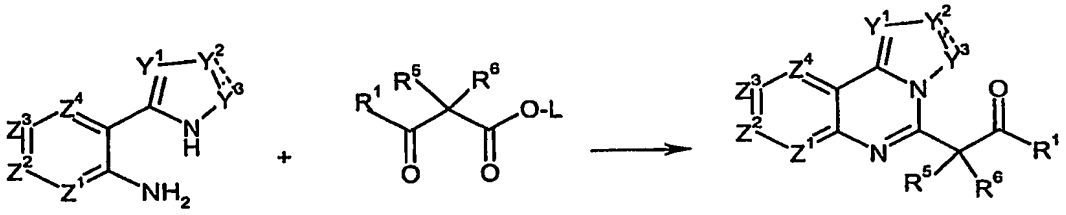
The compound of the formula (I-a)



I-a

(wherein R^1, R^5, R^6, Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) can be, but not limited to be, prepared by the following Reaction A.

Reaction [A]



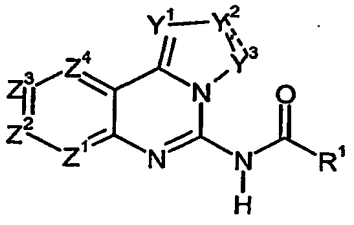
II III I-a

The compound (I-a) can be prepared, for example, by the reaction of the compound of formula (II) (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) with a compound (III) (wherein R^1, R^5 and R^6 are the same as defined above, and L represents C_{1-6} alkyl).

The reaction may be carried out without solvent, or in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethyl-acetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol,; water, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 10 C to 200 C and preferably about 50 C to 160 C. The reaction may be conducted for, usually, 10 minutes to 48 hours and preferably 30minutes to 24 hours.

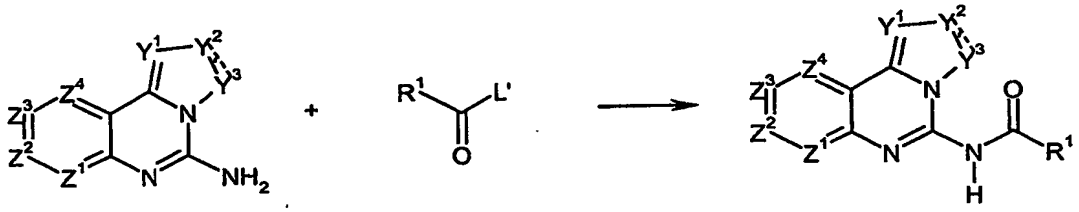
Alternatively, the compound of the formula (I-b):



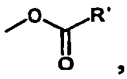
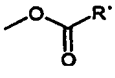
I-b

(wherein R^1, Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) can be, but not limited to be, prepared by the following Reaction B.

Reaction [B]



IV V I-b

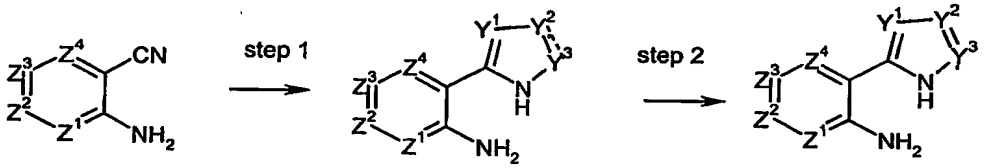
The compound (I-b) can be prepared, for example, by the reaction of the compound of formula (IV) (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) with a compound of formula (V) (wherein R^1 is the same as defined above and L' is a leaving group, such as hydroxy; halogen atom e.g., chlorine, bromine, or iodine atom; or  , wherein R^1 is the same as defined above.) In the case L' is hydroxy, the reaction can be advantageously carried out by using a coupling agent such as benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), 1,1'-carbonyldi(1,3-imiazole)(CDI), 1,1'-carbonyldi(1,2,4-triazole)(CDT) and others. In the case L' is halogen atom or  the reaction can be advantageously conducted in the presence of a base, including, for instance, such as pyridine, triethylamine and N,N-diisopropylethylamine, dimethylaniline, diethylaniline, and others.

The reaction may be carried out without solovent, or in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about 40 C to 200 C and preferably about 20 C to 180 C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

Preparation of intermediates

The compound of formula (II') (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above and Y^2 and Y^3 are connected by single bond) and the compound of formula (II") (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above and Y^2 and Y^3 are connected by double bond) can be prepared by the following procedures.



VI II' II"

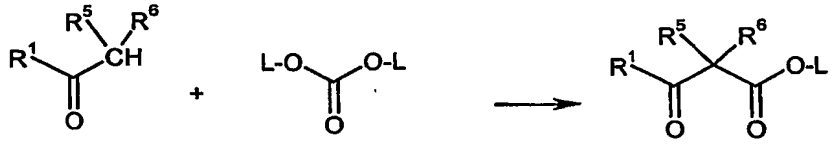
In the step 1, the compound (II') (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above and Y^2 and Y^3 are connected by single bond) can be prepared, for example, by the reaction of the compound of formula (VI) (wherein Z^1, Z^2, Z^3 and Z^4 are the same as defined above) with an diaminoalkane derivatives such as ethylenediamine. The reaction can be advantageously carried out using appropriate dehydrating agents such as $SOCl_2$, $POCl_3$, P_2O_5, P_2S_5, and others. The reaction may be carried out without solovent, or in a solvent including for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used. The reaction temperature is usually, but not limited to, about 10 C to 200 C and preferably about 50 C to 200 C. The reaction may be conducted for, usually, 10 minutes to 48 hours and preferably 30minutes to 24 hours.

In the step 2, the compound (II'') (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above and Y^2 and Y^3 are connected by double bond) can be prepared, for example, from the compound of formula (II') (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above and Y^2 and Y^3 are connected by single bond) by the oxidation reaction using an agent such as MnO_2, $KMnO_4$ and others, or by the dehydrogenation reaction using palladium on carbon.

The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; dimethylformamide (DMF), dimethylacetamide(DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used. The reaction temperature is usually, but not limited to, about 0 C to 200 C and preferably about 50 C to 200 C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 24 hours.

The compound (VI) is commercially available or can be synthesized by conventional method.

The compound of formula (III) can be prepared, for example, by the following procedures.



VII VIII III

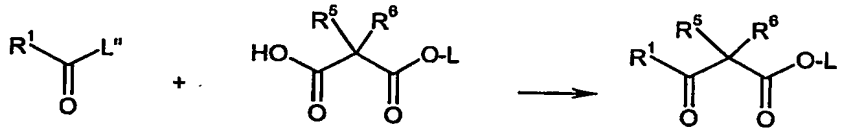
The compound (III) (wherein L, R^1, R^5 and R^6 are the same as defined above) can be prepared by the reaction of the compound of formula (VII) (wherein R^1, R^5 and R^6 are the same as defined above) with the compound of formula (VIII) (wherein L is

the same as defined above) in the presence of a base such as potassium hydride, potassium hexamethyldisilazide, and others.

The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene, dimethylformamide (DMF), dimethylacetamide(DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about -100 C to 100 C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

Alternatively, the compound (III) (wherein L, R^1, R^5 and R^6 are the same as defined above) can be prepared by the reaction of the compound of formula (IX) (wherein R^1 is the same as defined above and L" is a leaving group, such as halogen atom e.g., chlorine or bromine atom) with the compound of formula (X) (wherein wherein L, R^5 and R^6 are the same as defined above)

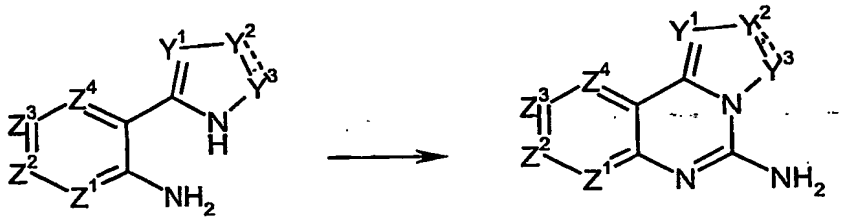


IX X III

The reaction can be carried out in the presence of a base such as n-butyl lithium, sec-butyl lithium, and others. The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The compound (VII), (VIII), (IX) and (X) are commercially available or can be synthesized by conventional method.

The compound of formula (IV) can be prepared by the following procedures:



II IV

The compound of formula (IV) (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) can be prepared by the reaction of compound (II) (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) with cyanogen halides such as cyanogen bromide.

The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol; and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about -10°C to 200°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 hour to 24 hours.

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon(s) in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

Typical salts of the compound shown by the formula (I) include salts prepared by the reaction of the compound of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tri(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salts thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols

and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions,

emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxy-methyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and a sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01mg/kg/day to about 100mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In case of parenteral administration, it has generally proven advantageous to administer quantities of about 0.001 to 100 mg/kg/day, preferably from 0.01 mg/kg/day to 1mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

Examples

The present invention will be described in detail below in the form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

^{1}H NMR spectra were recorded using either Bruker DRX-300 (300 MHz for ^{1}H) spectrometer or Brucker 500 UltraShieled™ (500 MHz for 1H). Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constant (J) are given in hertz and the abbreviations s, d, t, q, m, and br refer to singlet, doublet, triplet, quartet, multiplet, and broad, respectively. The mass determinations were carried out by MAT95 (Finnigan MAT).

Liquid Chromatography - Mass spectroscopy (LC-MS) data were recorded on a Micromass Platform LC with Shimadzu Phenomenex ODS column(4.6 mm ϕ X 30 mm) flushing a mixture of acetonitrile-water (9:1 to 1:9) at 1 ml/min of the flow rate. Mass spectra were obtained using electrospray (ES) ionization techniques (Micromass Platform LC). TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150 μm)) was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Tokyo kasei kogyo Co., Ltd., Nacalai tesque, Inc., Watanabe Chemical Ind. Ltd., Maybridge plc, Lancaster Synthesis Ltd., Merck KgaA, Kanto Chemical Co., Ltd.

The effects of the compounds of the present invention were examined by the following assays and pharmacological tests.

[Determination of IC50 values of compounds in kinase assay of PI3Kγ]

Chemicals and assay materials

Phosphatidylinositol (PtdIns) and phosphatidylserine (PtdSer) were purchased from DOOSAN SERDARY RESEARCH LABORATORIES (Toronto, Canada). Recombinant human PI3Kγ (full length human PI3K p110γ fused with a His_6-tag at the C-terminus expressed in *S. frugiperda* 9 insect cells) was obtained from ALEXIS BIOCHEMICALS (#201-055-C010; San Diego, CA). [γ^{33}P]ATP and unlabeled ATP were purchased from AMERSHAM PHARMACIA BIOTECH (Buckinghamshire, UK) and ROCHE DIAGNOSTICS (Mannheim, Germany), respectively. Scintillation cocktails, MicroScint PS™ and Optiplates™ were purchased from PACKARD (Meriden, CT). Maxisorp™ plates and Nunclon Delta™ plates were purchased from NALGE NUNC INTERNATIONAL K.K. (Tokyo, Japan). All other chemicals not further specified were from WAKO PURE CHEMICALS (Osaka, Japan).

Solid-Phase Lipid Kinase Assay

To assess inhibition of PI3Kγ by compounds, the Maxisorp™ plates were coated with 50 µl/well of a solution containing 50 µg/ml PtdIns and 50 µg/ml PtdSer dissolved in chloroform:ethanol (3:7). The plates were subsequently air-dried by incubation for at least 2 hours in a fume hood. The reaction was set up by mixing 25 µl/well of assay buffer 2x (100 mM MOPSO/NaOH, 0.2 M NaCl, pH 7.0, 8 mM $MgCl_2$, 2 mg/ml BSA (fatty acid-free)) and 50 ng/well PI3Kγ in the lipid pre-coated plate and 10x test compounds were added in 2% DMSO. The reaction was started by adding 20 µl/well of ATP mix (final 10 µM ATP; 0.05 µCi/well [γ^{33}P]ATP). After incubation at RT for 2 hours, the reaction was terminated by adding 50 µl/well stop solution (50 mM EDTA, pH 8.0). The plate was then washed twice with Tris–buffered saline (TBS, pH 7.4). MicroScint PS™ (PACKARD) scintillation mix was added at 100 µl/well, and radioactivity was counted by using a TopCount™ (PACKARD) scintillation counter.

The inhibition percent at each concentration of compound was calculated, and IC50 values were determined from the inhibition of curve.

[Isozyme selectivity test in PI3K]

{Determination of IC50 values of compounds in kinase assay of PI3Kβ}

Recombinant baculovirus of PI3Kβ p110β and GST-p85α were obtained from Dr. Katada (University of Tokyo). Recombinant PI3K heterocomplex of p110β and GST-p85α were co-expressed in insect cells according to manufacture's instruction (Pharmingen, San Diego, CA), and purified with glutathione affinity column. Kinase assay of PI3Kβ is prepared in a similar manner as described in the part of [Determination of IC50 values of compounds in kinase assay of PI3Kγ].

[Selectivity test with other kinases]

Kinase selectivity of compounds was assessed by using kinase assay of IKK-β, syk and MKK7.

{IKK-β kinase inhibitory assay}

(1) Preparation of IKK-β kinase protein

A cDNA fragment encoding human IKK-β open reading frame was generated by PCR with the use of a pair of primers designed from the published sequence (Woronicz JD et al. (1997) Science 278, 866-869). A template was obtained from Quickclone cDNA (Clontech) using Elongase™ Amplification kit (Life Technologies). The DNA fragments generated by PCR were gel-purified and subcloned into pBluescript. The cDNA fragment cloned in pBluescript was inserted into pcDNA3.1/His C KpnI/NotI, and transferred into pVL1393 SmaI/XbaI (Pharmingen) to construct a baculovirus transfer

vector. Then the vector, together with the linearized baculovirus (BaculoGold™, Pharmingen) was used to transfect Sf21 cells (Invitrogen, San Diego, CA). Generated recombinant baculovirus was cloned and amplified in Sf21 cells, grown in TNM-FH insect cell medium (Life Technologies, Inc.) supplemented with 10% FCS, 50 g/ml Gentamycin, 0.1% Pluronic F-68 (Life Technologies, Inc.) as suspension culture (200 ml in 1 L Erlenmeyer flask; 27°C; 130 rpm). Sf21 cells were infected with this amplified virus with a multiplicity of infection of 5 following standard protocols (Crossen R, Gruenwald S (1997) Baculovirus Expression Vector System Instruction Manual, Pharmingen Corporation) and harvested 48 hours later. The cells were lysed to obtain the produced chimeric protein of IKK-β kinase fused by histidine (His-tagged IKK-beta).

(2) The preparation of purified GST-IκBα fusion proteins

An expression vector containing the nucleotide sequence encoding fusion protein of GST with amino acid residues 1 to 54 of IκBα under the control of an IPTG-inducible promoter was constructed. The expression vector was introduced in E. coli and the transformant was cultured and lysed to obtain a GST-IκBα fusion protein. Then the resulting GST-IκBα fusion protein was purified and biotinated for kinase assay.

(3) The measurement of IKK-β kinase activity

The 96-well format kinase assay of IKK-β was performed to test the inhibitory activity of the compounds of the present invention. First, 5 µl of a test compound was put in the presence of 2.5% dimethyl sulfoxide (DMSO) in each well in a U-bottomed 96-well plate (Falcon). For control wells of background (BG) and total phosphorylation (TP), 5 µl of 2.5% DMSO was put. Recombinant IKK-β (final 0.6 µg/ml) and bio-GST-IκBα (1-54) (final 0.2 µM) were diluted in 25 µl of 2 x kinase buffer β (40 mM Tris-HCl, pH

7.6, 40 mM $MgCl_2$, 40 mM β-glycerophosphate, 40 mM p-nitrophenyl-phosphate, 2 mM EDTA, 40 mM creatine phosphate, 2 mM DTT, 2 mM Na_3VO_4, 0.2 mg/ml BSA and 0.8 mM phenylmethylsulfonyl fluoride) and transferred to the 96-well plate. Bio-GST-IκBα (1-54) in 25 µl of 2 x kinase buffer β without IKK-β was transferred to BG wells. Then 20 µl of 12.5 µM ATP, 62.5 µCi/ml [γ-^{33}P] ATP (Amersham Pharmacia Biotech) was added and the resulting mixture was incubated for 2 hours at room temperature. The kinase reactions were terminated by the addition of 150 µl of termination buffer (100 mM EDTA, 1 mg/ml BSA, 0.2 mg NaN_3). One handred and fifty µl of the sample were transferred to a streptavidin-coated, white MTP (Steffens Biotechniche Analysen GmbH #08114E14.FWD) to capture the biotinylated substrates. After 1 hour of incubation, non-bound radioactivity was eliminated by washing the wells five times with 300 µl of washing buffer including 0.9 % NaCl and 0.1% (w/v) Tween-20 with the use of a MW-96 plate washer (BioTec). The bound radioactivity was determined after the addition of 170 µl MicroScint-PS scintillation cocktail (Packard) using a TopCount scintillation counter.

{Syk tyrosine kinase inhibitory assay for selectivity}

(1) Preparation of Syk protein

A cDNA fragment encoding human Syk openreading frame was cloned from total RNA of human Burkitt's lymphoma B cell lines, Raji (American Type Culture Collection), with the use of RT-PCR method. The cDNA fragment was inserted into pAcG2T (Pharmingen, San Diego, CA) to construct a baculovirus transfer vector. Then the vector, together with the linearized baculovirus (BaculoGoldTM, Pharmingen), was used to transfect Sf21 cells (Invitrogen, San Diego, CA).

Generated recombinant baculovirus was cloned and amplified in Sf21 cells. Sf21 cells were infected with this amplified high titer virus to produce a chimeric protein of Syk kinase fused by glutathione-S-transferase (GST).

The resulting GST-Syk was purified with the use of glutathione column (Amersham Pharmacia Biotech AB, Uppsala, Sweden) according to the manufacturer's instruction. The purity of the protein was confirmed to be more than 90% by SDS-PAGE.

(2) Synthesize of a peptide

Next, a peptide fragment of 30 residues including two tyrosine residues, KISDFGLSKALRADENYYKAQTHGKWPVKW, was synthesized by a peptide synthesizer. The N-terminal of the fragment was then biotinylated to obtain biotinylated activation loop peptide (AL).

(3) The measurement of Syk tyrosine kinase activity

All reagents were diluted with the Syk kinase assay buffer (50 mM Tris-HCl (pH 8.0), 10 mM $MgCl_2$, 0.1 mM Na_3VO_4, 0.1% BSA, 1 mM DTT). First, a mixture (35 µl) including 3.2 µg of GST-Syk and 0.5 µg of AL was put in each well in 96-well plates. Then 5µl of a test compound in the presence of 2.5% dimethyl sulfoxide (DMSO) was added to each well. To this mixture was added 300 µM ATP (10 µl) to initiate the kinase reaction. The final reaction mixture (50 µl) consists of 0.65 nM GST-Syk, 3 µM AL, 30 µM ATP, a test compound, 0.25% DMSO, and a Syk kinase assay buffer.

The mixture was incubated for 1 hour at room temperature (RT), and the reaction was terminated by the addition of 120 µl of termination buffer (50 mM Tris-HCl (pH 8.0), 10 mM EDTA, 500 mM NaCl, 0.1% BSA). The mixture was transferred to streptavidin-coated plates and incubated for 30 minutes. at room temperature to

combine biotin-AL to the plates. After washing the plates with Tris-buffered saline (TBS) (50 mM Tris-HCl (pH 8.0), 138 mM NaCl, 2.7 mM KCl) containing 0.05% Tween-20 for 3 times, 100 µl of antibody solution consisting of 50 mM Tris-HCl (pH 8.0), 138 mM NaCl, 2.7 mM KCl, 1% BSA, 60 ng/ml anti-phosphotyrosine monoclonal antibody, 4G10 (Upstate Biotechnology), which was labeled with europium by Amersham Pharmacia's kit in advance, was added and incubated at room temperature for 60 minutes. After washing, 100 µl of enhancement solution (Amersham Pharmacia Biotech) was added and then time-resolved fluorescence was measured by multi-label counter ARVO (Wallac Oy, Finland) at 340 nm for excitation and 615 nm for emission with 400 msec of delay and 400 msec of window.

{The measurement of MKK7 kinase activity}

(1) Preparation of MKK7 protein

A plasmid containing human MKK7 open reading frame was cloned into a pGEM-T Easy vector (Promega, Madison, WI) and further into a pGEX-6P-2 vector (Pharmacia) to construct human GST(Glutathione-S-transferase)-MKK7 fusion protein. This construct was coexpressed with human MEKKc (catalytic domain of MEKK (MEK (Map kinase kinase) kinase) on plasmid pBB131, in E.coli (BL21(DE3)pLysS).

The resulting GST-MKK7 was purified with the use of a glutathione column (Amersham Pharmacia Biotech AB, Uppsala, Sweden) according to the manufacturer's instructions.

(2) A construct containing the MKK7 substrate rat GST-KN-SAPKα (GST + kinase negative rat SAPKα2) was inserted into a pGEX-SAP plasmid (Amersham Pharmacia Biotech AB, Uppsala, Sweden) and transformed into E.coli BL21(DE3)pLysS. Using this expression strain, GST-KN-SAPKα was purified with the use of glutathione column (Amersham Pharmacia Biotech

AB; Uppsala, Sweden) according to the manufacturer's instruction. The purity of the protein was confirmed to be more than 90% by SDS-PAGE. Biotinylation of the substrate protein was done using sulfo-NHS-LC Biotin according to the manufacturer's instructions (Pierce, Rockford, US)

(3) The measurement of MKK7 kinase activity

All Test compounds (2.5 µl) at various concentrations (in 1% DMSO) were added to 15 µl of reaction buffer (20mM HEPES, 0.1M NaCl, 0.1mM Na_3VO_4, 10mM $MgCl_2$, 1mM DTT, 1mg/ml BSA, pH 7.5)) containing 0.5 µg/ml GST-MKK7 and 0.8 µM SAPK α (biotinylated GST-KN-SAPKα fusion protein). The kinase reaction was started by the addition of 12.5µl of 12 µM ATP. After one hour incubation period at room temperature, the reaction was stopped by the addition of 40 µl stop solution (0.1M EDTA, pH 8.0).

60 µl of this reaction mixture were transferred to a well of the streptavidine-coated detection plate (SA-plate, Steffens: 08114E14.FWD) and 40 µl Tris-buffered saline (TBS, 50 mM Tris-HCl (pH8.0), 20 mM EDTA, 1 % BSA, 1 M NaCl, 0.05% tween 20) were added. This mixture was incubated for 30 minutes and washed 3 times with 0.05% tween20 in (TBS), before 100 µl of Eu-labeled anti-phosphothreonine-proline antibody (LANCE) was added. After incubation for 30 minutes, plates were again washed 3 times with TBS, and 100 µl of the enhancement solution (Amersham Pharmacia Biotech) was added. One hour later, time-resolved fluorescence was measured by a multi-label counter (ARVO, Wallac Oy, Finland) using 340 nm for excitation and 615 nm for emission with 400 ms of delay and 400 ms of window.

[Determination of IC50 values of compounds in superoxide generation from human peripheral mononuclear cells]

Blood (100 ml/donor) was taken from healthy human volunteers by venepuncture with 50 ml syringes containing 50 units heparin. Red blood cells were removed by incubation with 1% (w/v) dextran and 0.45% (w/v) glucose for 30 minutes at room temperature. After centrifugation at 350 xg for 10 minutes, precipitation was suspended in 10 ml PBS. The cell suspension was gently layered on 20 ml of 60% phase and 20ml of 80% phase of Percoll (Amersham Pharmacia Biotech, Sweden) gradient in PBS in 50 ml tube (#2335-050, Iwaki, Japan). After centrifugation at 400 xg for 30 minutes at room temperature, peripheral polymorphonuclear leukocytes (PMNs) were obtained from an interference between 60% and 80% Percoll phases. After twice washing in PBS, PMNs were suspended at 10^7 cells/ml in Hank's Balanced Salt Solution (HBSS: Nissui, Japan) supplemented by 10 mM Na-Hepes (pH 7.6), 0.1% BSA and kept on ice until experiments.

To test inhibition of fMLP-induced superoxide generation by compounds, PMNs (5 x 10^5 cells/well) were seeded in HBSS, 10 mM Na-Hepes (pH 7.6), 0.1% BSA in 96-well clear bottom black plate (Cat.#3904, Costar). And cells were pretreated with luminol (1 μg/well; Sigma) and test compounds for 10 minutes at 37°C. fMLP peptede (Cat.#4066; Peptide Institute Inc, Japan) were prepared at 10 μM in the same buffer and prepared into a polypropylene plate (Cat.#3365, Coster). Chemi-luminescence (CL) was measured by FDSS-6000 (Hamamatsu Photonics) over 15 minutes after the stimulation with 1 μM fMLP. The inhibition percent at each concentration of compound was calculated of first peak of CL at approximately 1 minute after addition of stimuli, and IC50 values were determined from the inhibition of curve.

For opsonized zymosan (OZ) and phorbol 12-myristate 13-acetate (PMA) stimulation, Zymosan A (Sigma) was suspended in HBSS at a concentration of 1 mg/ml and incubated with human pooled serum at a final concentration range of 9 to 80% at 37°C for 30 minutes to opsonize the zymosan, followed by centrifugation at 500×g for 10 minutes at 4°C. Then the sediments were washed twice in HBSS and finally resuspended in HBSS to a concentration between 1 and 10 mg/ml. OZ was used at

5 mg/ml for stimulation. PMA was initially dissolved at a concentration of 0.1 mg/ml in DMSO as a stock solution and stored frozen at -20°C. PMA solution was prepared from the stock solution by further dilution in HBSS to the concentration of 100 ng/ml. PMNs (5 x 10^5 cells/well) were seeded in HBSS, 10 mM Na-Hepes (pH 7.6), 0.1% BSA in 96-well white plate (Packard). And cells were pretreated with luminol (1 μg/well; Sigma) and test compounds for 10 minutes at 37°C. Luminescence was measured by Arvo counter (Wallac)) at 30 minutes after the stimulation with OZ or PMA. The inhibition percent at each concentration of compound was calculated and IC50 values were determined from the inhibition of curve.

[Determination of IC50 values of compounds in elastase release from human peripheral mononuclear cells]

To test inhibition of elastase release by compounds, PMNs (5 x 10^5 cells/well) were seeded in HBSS supplemented with 10 mM Na-Hepes (pH 7.6), 0.1% BSA in 96-well plate. Cells were pretreated with cytocharasine B (0.1 μg/well; Nakarai, Japan) and test compounds in 90 μl/well for 10 minutes at 37°C. Cells were stimulated with 1 μM fMLP for 15 minutes at 37°C. Supernatants (40 μl/well) were collected into 384 well black plate (Packard) to measure elastase activity. Fluorescent-based elastase reaction was stared by addition of 10 μl of 0.5 mM Suc-Ala-Ala-Ala-MCA (Cat. #3133v; Peptide Institute Inc, Japan) into the 384 well plate at room temperature. The fluorescence emission was measured at 460 nm (λex, 360 nm) by using a Wallac-Arvo counter (PerkinElmer, Boston, MA) fluorescence plate leader for 120 minutes. IC50 values of compounds were determined at initial velocity of the reaction.

[Determination of IC50 values of compounds in chemotaxis assay with the use of human PMNs]

Freshly prepared PMNs (1.1 x 10^7 cells/ml) were incubated with compounds in a polypropylene 96 well plate (Cat.#3365, Coster) for 10 minutes in HBSS supplemented with 10 mM Na-Hepes (pH 7.6), 0.1% BSA. Cells (100 µl) were incubated with test compounds or vehicle for 30 minutes and were transferred into an Multiwell insert (Cat.# 351183; Falcon) 24w plate. FMLP (10 nM, 0.5 ml) was added into the lower chamber of plate. Cells are allowed chemotaxis in CO_2 incubator at 37°C for 1 hour. Migrated cells were counted using FACScan (Becton Dickinson, Franklin Lakes, NJ). The inhibition percent at the each concentration of compound was calculated, the IC50 values were determined from the inhibition curve.

[Determination of IC50 values of compounds in chemotaxis assay with the use of human eosionphils]

(1) cell

Human CCR3-transformed L1.2 cells were used. Human CCR3-expressing L1.2 stable transformant was established by electroporation, referring to the methods described in J. Exp. Med. 183:2437-2448, 1996. The human CCR3-transformed L1.2 cells were maintained in RPMI-1640 supplemented with 10% FCS , 100 units/ml of penicillin G and 100 µg/ml of streptomycin, and 0.4 mg/ml of Geneticin. One day before the chemotaxis assay, cells were pretreated with 5 mM sodium butyrate -containing culture medium (5 x 10^5cells/ml) for 20-24 hours to increase the expression of CCR3.

(2) Chemotaxis assay

Butyrate-pretreated cells were suspended in chemotaxis buffer (Hanks' solution Cat.#05906 Nissui, 20 mM HEPES pH 7.6, 0.1% human serum albumin Cat.#A-1887 Sigma) at a cell density of 1.1 x 10^7 cells /ml. A mixture of 90 µl of cell suspension and 10 µl of compound solution diluted with chemotaxis buffer (10-times concentration of the final concentration)

were preincubated for 10 minutes at 37°C. The mixture of cells and compounds was added into the upper chamber of the 24-well chemotaxis chamber (Transwell™, Cat.#3421, Costar, pore size;5 μm). 0.5 ml of 10 nM of human recombinant eotaxin(Cat.#23209, Genzyme Techne) solution, diluted with chemotaxis buffer, was added into the lower chamber of the chemotaxis plate. Then, chemotaxis was performed in CO_2 incubator at 37°C for 4 hours. After 4hours incubation, migrated cells were counted using FACScan (Becton Dickinson). The inhibition percent at the each concentration of compound was calculated, and IC50 values were determined from the inhibition curve.

[Mouse fMLP-induced pleuricy Model]

Seven weeks old BALB/c female mice were placed into 3 groups, a nontreatment group, a vehicle group and a treated group. Mice in the treated group were first injected intravenously with compounds of the present invention at varied doses. Mice in the vehicle group were injected with vehicle containing 10% Cremophor EL (Nacalai Tesque) in saline. Three minutes after the treatment, a solution containing 1 mg/mouse of fMLP in 3.3% DMSO in PBS was administrated intrapleuraly into a vehicle group and a treated group mice. Four hours after fMLP-injection, mice were sacrificed and pleural fluid was collected by washing the pleural cavity twice with 2 ml PBS. Total cells per milliliter of pleural fluid was counted using a hemacytometer. Cell differentiation of pleural fluid was determined by counting a minimum of 200 cells from a Giemsa's stained cytospin slide preparation. Statistic analysis was performed by means of Student's T test for paired data or analysis of variance with Dunnett's Post test , using GraphPadPRISM for Windouws, version 2.01.

For practical reasons, the compounds are grouped in some classes of activity as follows:

In vitro IC_{50} = A 0.5μM < B 2 μM < C 10 μM < D

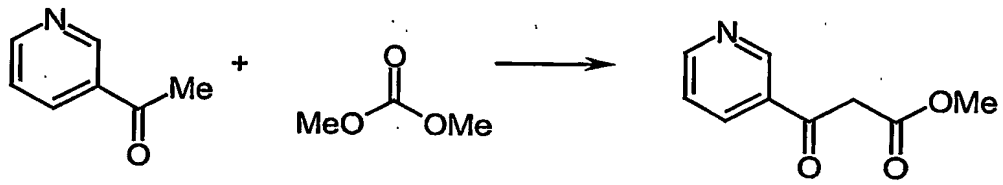
Cellular IC_{50} = A 1μM < B 10 μM < C

The compounds of the present invention also show excellent selectivity, and strong activity in vivo assays.

(dec.) in the following tables represents decomposition.

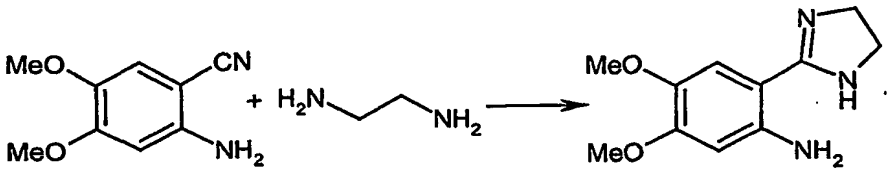
Example 1-1

(1) Methyl 3-oxo-3-(3-pyridinyl)propanoate



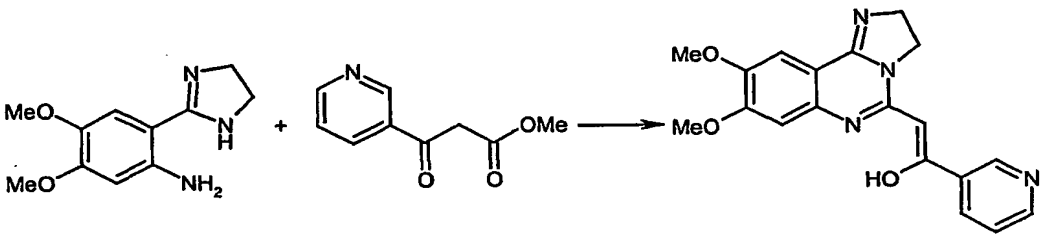
A 0.5 M solution of pottasium hexamethyldisilazide in toluene (22 ml, 11 mmol) was mixed with tetrahydrofuran (5 ml), and the mixture was cooled at -78°C. To the cold (-78°C) mixture was added dropwise a solution of 3-acethylpyridine (1.0 g, 8.26 mmol) in tetrahydrofuran (5 ml). The mixture was warmed to room temperature and stirred for 3 hours. The mixture was cold at -78°C, and then dimethyl carbonate (1.2 ml, 14.3 mmol) was added dropwise. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction solution was quenched by adding aqueous 1N HCl solution, and extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtrated, and concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel (hexane/ ethyl acetate, 1/1) to give methyl 3-oxo-3-(3-pyridinyl)propanoate (1.0 g, 68% yield) as an oil.

(2) 2-(4,5-Dihydro-1H-imidazol-2-yl)-4,5-dimethoxyaniline:



2-Amino-4,5-dimethoxybenzonitrile (5.0 g, 28 mmol) was added to ethylene-diamine (7.9 g, 131 mmol) at room temperature. The resulting solution was warmed to 40., and a catalitic amount of diphosphorus pentasulfide (50 mg) was added. The mixture was heated to 80-90 ., and the stirring was continued overnight. The reaction mixture was diluted with water, and the resulting precipitae was collected by filtration to give 2-(4,5-dihydro-1H-imidazol-2-yl)-4,5-dimethoxyaniline (5.1 g, 82 %) as a solid.

(3) (Z)-2-(8,9-Dimethoxy-2,3-dihydroimidazo[1,2-*c*]quinazolin-5-yl)-1-(3-pyridinyl)ethenol



A mixture of 2-(4,5-dihydro-1H-imidazol-2-yl)-4,5-dimethoxyaniline (0.15 g, 0.68 mmol) and methyl-3-oxo-3(3-pyridinyl)propanoate (0.20 g, 1.12 mmol) was stirred at 155. for 1 hour. The reaction mixture was purified by column chromatography on silica-gel (dichloromethane/ methanol, 25/1) to give (Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl) ethenol (66.9mg, 28%) as a yellow solid.

Melting point: 275°C

Molecular weight: 350.38

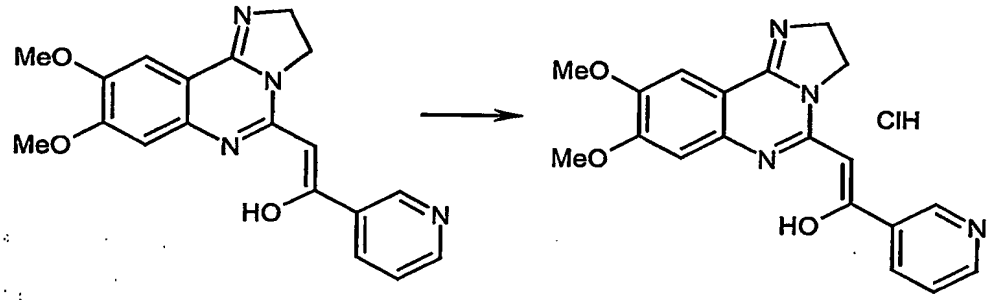
Mass spectrometry: 351 $(M + H)^+$

In vitro activity grade: A

^{1}H-NMR (500 MHz, DMSO-d6): d 3.79 (3H, s), 3.88 (3H, s), 3.98-4.08 (4H, m), 5.63 (1H, s), 7.13 (1H, s), 7.24 (1H, s), 7.50 (1H, dd, J = 4.7, 7.8 Hz), 8.27 (1H, dt, J = 1.6, 7.8 Hz), 8.67 (1H, dd, J = 1.6, 4.7 Hz), 9.13 (1H, d, J = 1.6 Hz), 13.9 (1H, bs).

Example 1-2

(*Z*)-2-(8,9-Dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)-ethenol hydrochloride



To a solution of (*Z*)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethenol (16.8 mg, 0.05 mmol)) in dioxane (15 ml) at room temperature was added aqueous 6N HCl solution (0.05 ml). After being stirrd for 30 minutes, the mixture was dried under reduced pressure to give (Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethenol ydrochloride (18.5 mg, quantitative) as a yellow solid.

Melting point: 275°C

Molecular weight: 386.84

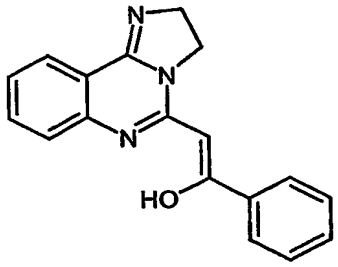
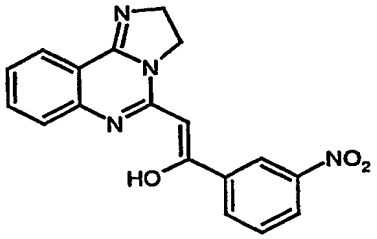
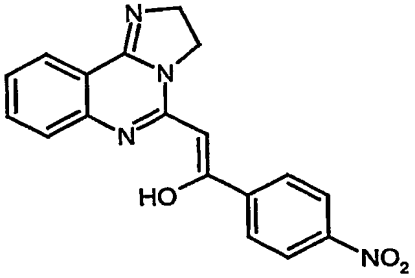
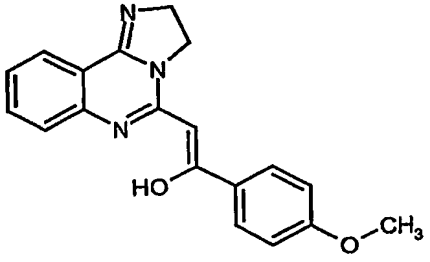
Mass spectrometry: 351 $(M + H)^+$

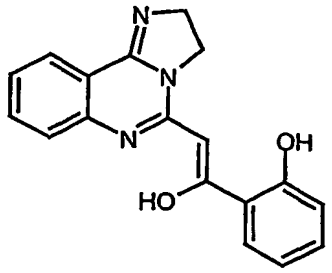
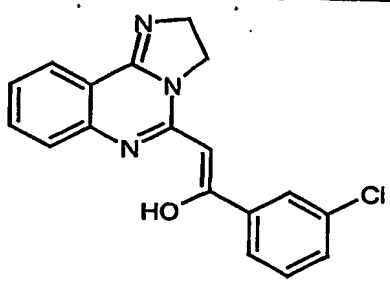
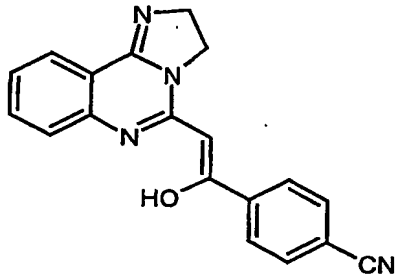
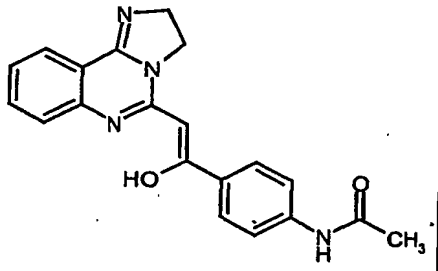
In vitro activity grade: A

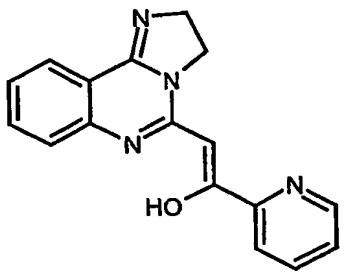
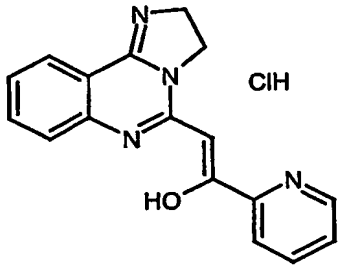
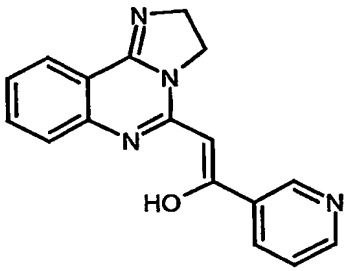
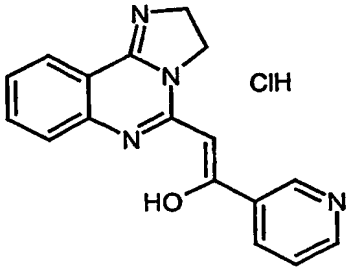
^{1}H-NMR (500 MHz, DMSO-d6): δ 3.88 (3H, s), 4.00 (3H, s), 4.22 (2H, t, J = 9.1 Hz), 4.55 (2H, t, J = 9.1 Hz), 6.21 (1H, s), 7.60 (1H, s), 7.66 (1H, dd, J = 4.7, 8.2 Hz), 7.90 (1H, s), 8.47 (1H, d, J = 8.2 Hz), 8.79 (1H, d, J = 4.7 Hz), 9.28 (1H, s), 14.9 (1H, bs).

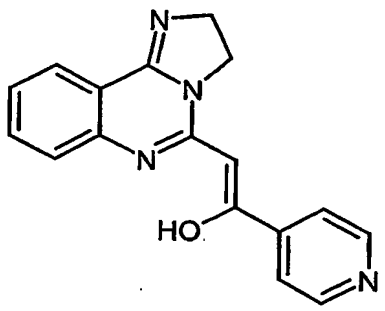
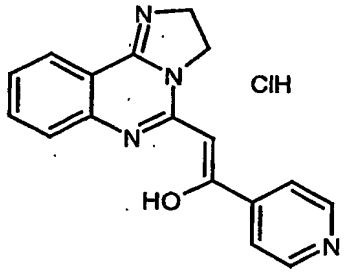
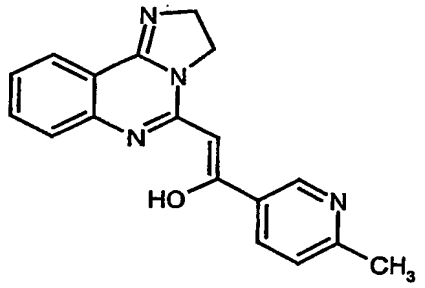
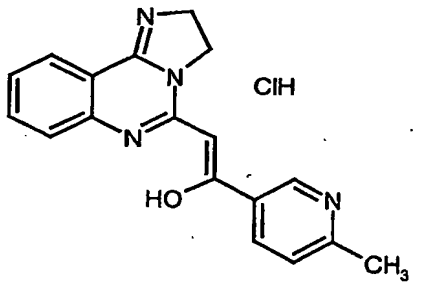
In a similar method according to the Example1-1 and 1-2 above, the compounds in Example 1-3 to 1-53 were synthesized.

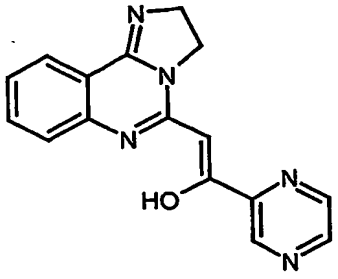
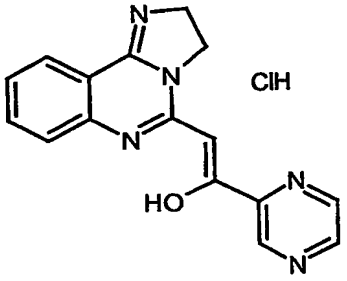
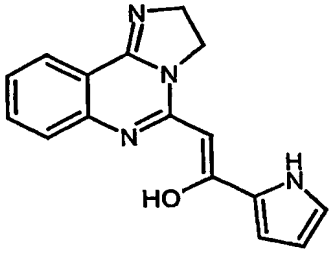
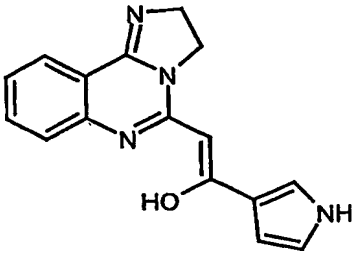
Table 1

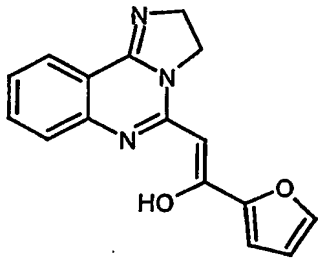
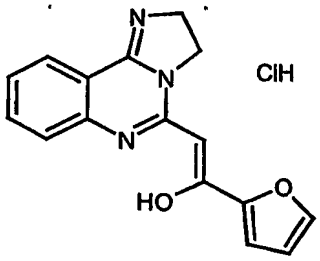
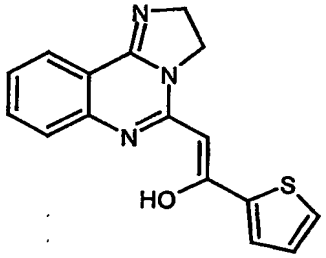
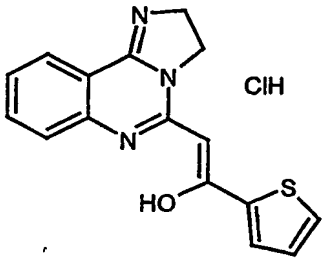
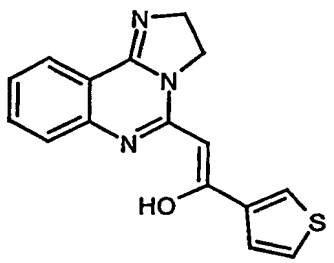
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-3		289,34	290	130-139	B
1-4		334,34	335	276	D
1-5		334,34	335	240-248	D
1-6		319,37	320	212-214	D

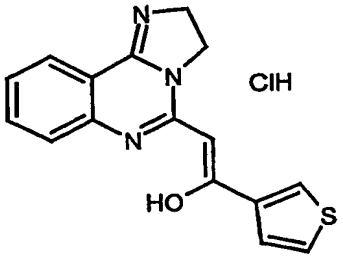
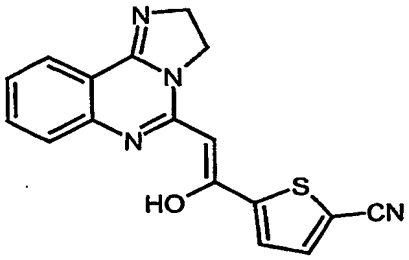
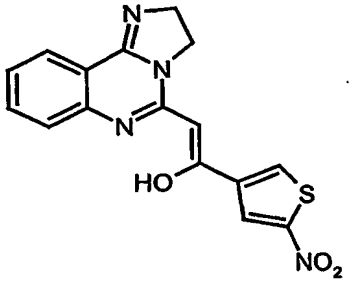
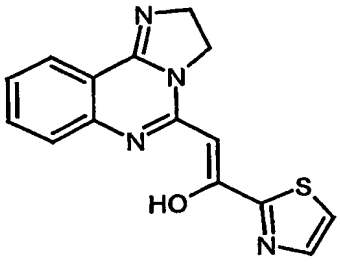
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-7		305,34	306	252-256	D
1-8		323,78	324	224-227	C
1-9		314,35	315	260-264	C
1-10		346,39	347	>300	A

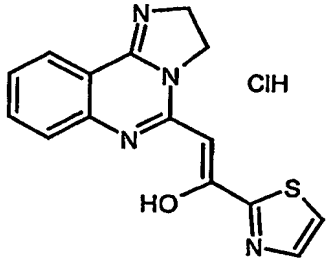
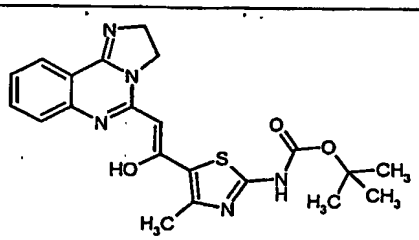
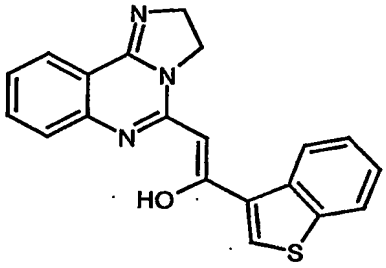
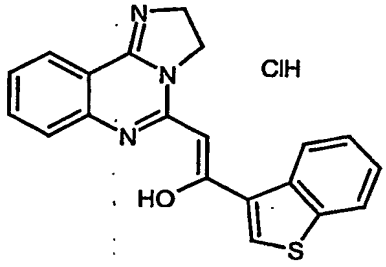
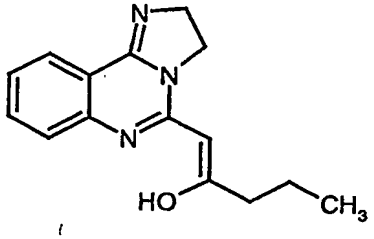
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-11		290,33	291	195	B
1-12		326,79	291	235-240	B
1-13		290,33	291	202	A
1-14		326,79	291	260(dec.)	A

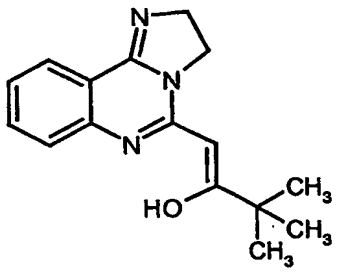
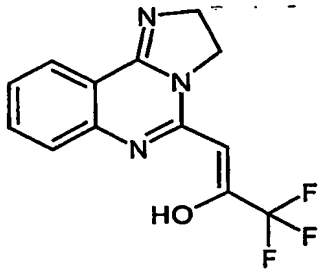
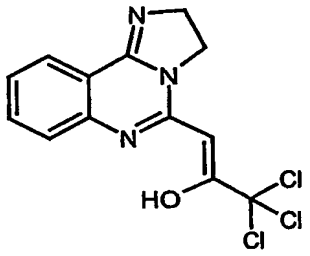
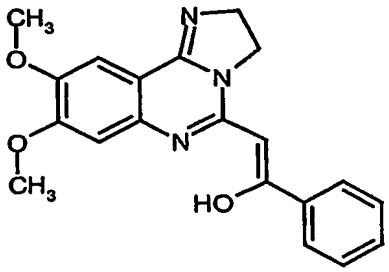
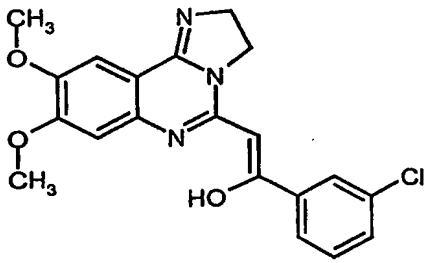
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-15		290,33	291	204-205	A
1-16		326,79	291	235(dec.)	A
1-17		304,35	305	217-219	A
1-18		340,82	305	amorphous	A

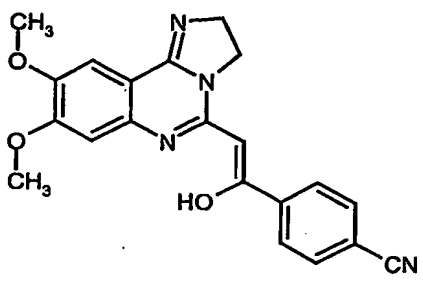
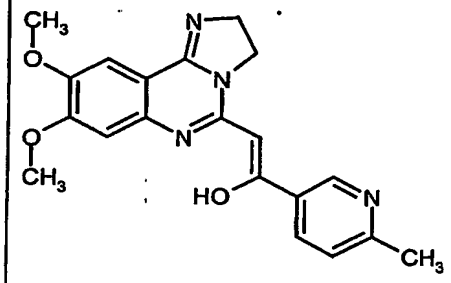
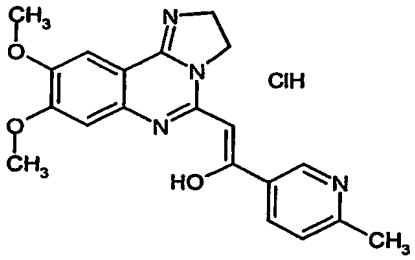
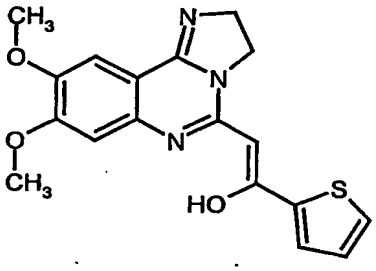
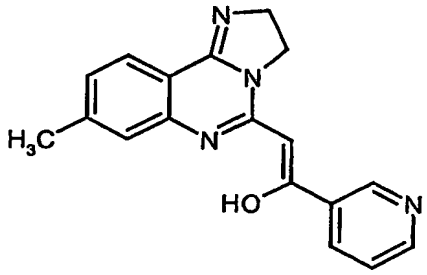
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-19		291,31	292	233-235	A
1-20		327,78	292	217-222	A
1-21		278,32	279	247	A
1-22		278,32	279	247-249	A

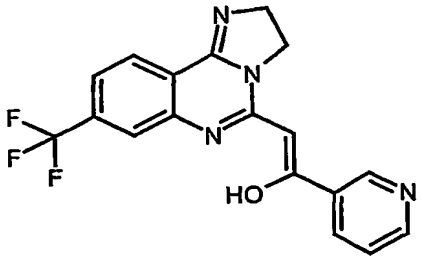
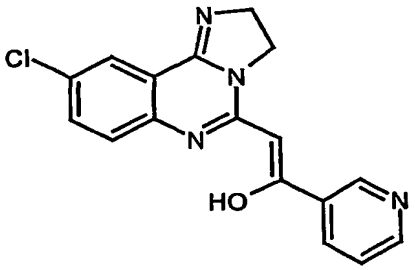
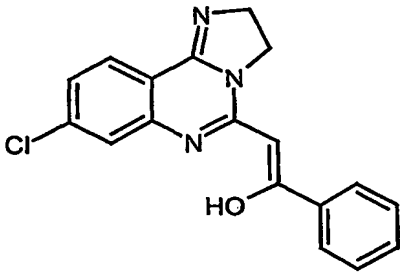
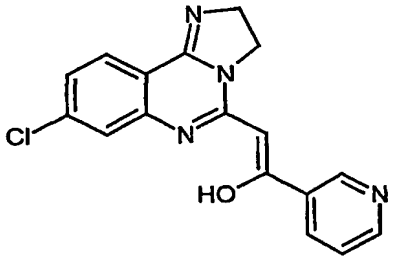
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-23		279,30	280	192	A
1-24		315,76	280	>300	A
1-25		295,37	296	193	A
1-26		331,83	296	>300	A
1-27		295,37	296	182-183	A

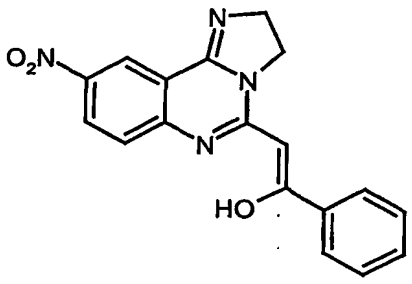
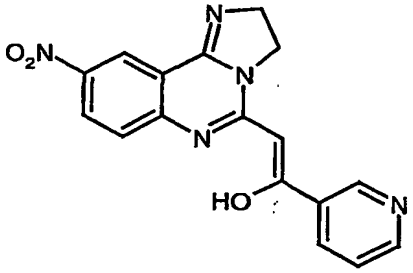
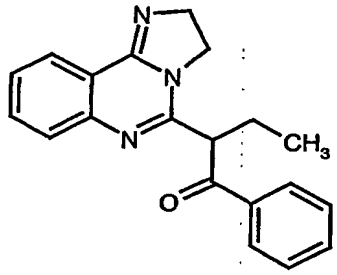
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-28		331,83	296	>300	A
1-29		320,38	321	256	B
1-30		340,36	341	255-258	D
1-31		296,35	297	208-210	A

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-32		332,81	297	> 300	A
1-33		425,51	426	>300	D
1-34		345,43	346	220-225	D
1-35		381,89	346	>300	C
1-36		255,32	256	113	C

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-37		269,35	270	134-138	B
1-38		281,24	282	240	B
1-39		330,60	330	190(dec.)	A
1-40		349,39	350	249-252	B
1-41		383,84	384	257-259	C

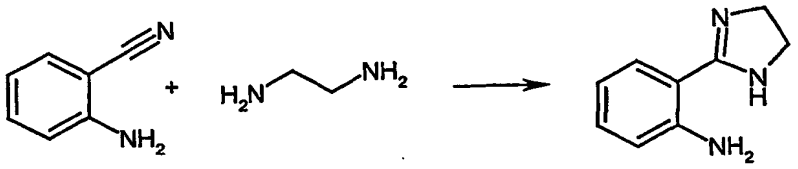
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-42		374,40	375	307-308	D
1-43		364,41	365	200-204	A
1-44		400,87	365	260(dec.)	A
1-45		355,42	356	250	A
1-46		304,35	305	224	A

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-47		358,33	359	264	B
1-48		324,77	325	260	B
1-49		323,78	324	186-188	B
1-50		324,77	325	226	A

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-51		334,34	335	259-262	C
1-52		335,32	336	306	B
1-53		317,39	318	156-160	D

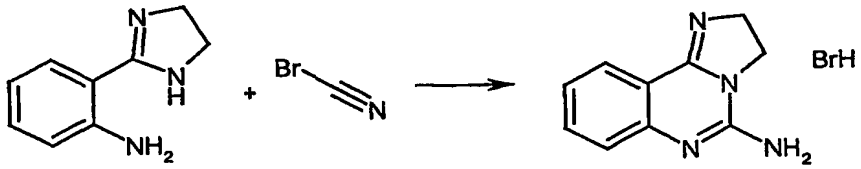
Example 2-1

(1) 2-(4,5-Dihydro-*1H*-imidazol-2-yl)aniline



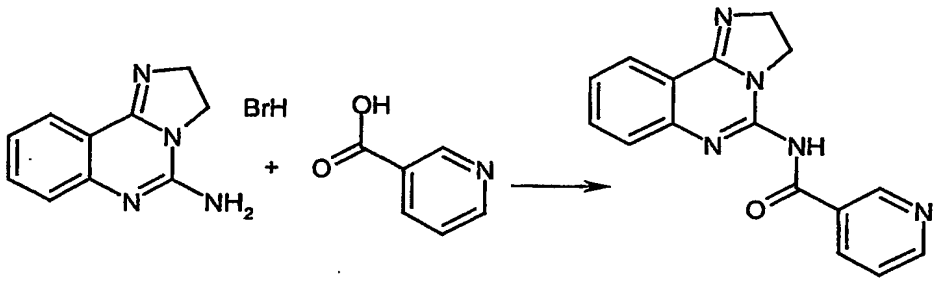
2-Aminobenzonitrile (9.00 g, 76.2 mmol) was added at 0°C to ethylenediamine (25.5 ml, 381 mmol) in small portions with stirring. After phosphorus pentasulfide (200 mg, 0.900 mmol) was added, the mixture was stirred at 100°C overnight. After cooling to 0°C, the reaction was diluted with water. The resulting white precipitate was collected by filtration, washed with water and diethyl ether, and dried under reduced pressure to give 2-(4,5-dihydro-1H-imidazol-2-yl)aniline (10.0 g, 81% yield).

(2) 2,3-Dihydroimidazo[1,2-c]quinazolin-5-ylamine hydrobromide



To a suspension of 2-(4,5-dihydro-1H-imidazol-2-yl)aniline (5.00 g, 31.0 mmol) in 85% methanol (60 ml) at 0°C was added cyanogen bromide (3.61 g, 34.1 mmol) by portions. This mixture was stirred at room temperature overnight. After the mixture was concentrated under reduced pressure, the resulting precipitate was collected by filtration. This pale green solid was washed with water, methanol and diethyl ether successively, and dried under reduced pressure to give 2,3-dihydroimidazo[1,2-c]quinazolin-5-ylamine hydrobromide (4.94 g, 60% yield).

(3) *N*-(2,3-Dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide



To a suspension of 2,3-dihydroimidazo[1,2-c]quinazolin-5-ylamine hydrobromide (500 mg, 1.87 mmol) and nicotinic acid (346 mg, 2.81 mmol) in *N,N*-dimethylformamide (25 ml) at room temperature was added benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (1.46 g, 2.81 mmol) followed by *N,N*-diisopropylethylamine (1.30 ml, 7.49 mmol). The mixture was heated at 80°C for 4 hours. After cooling to room temperature, the mixture was quenched with aqueous saturated $NaHCO_3$ solution. The resulting precipitate was collected by filtration, washed with water and diethyl ether, and dried under reduced pressure to give N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (450 mg, 83% yield).

Melting point: 238-239°C (decomposition)

Molecular weight: 291.31

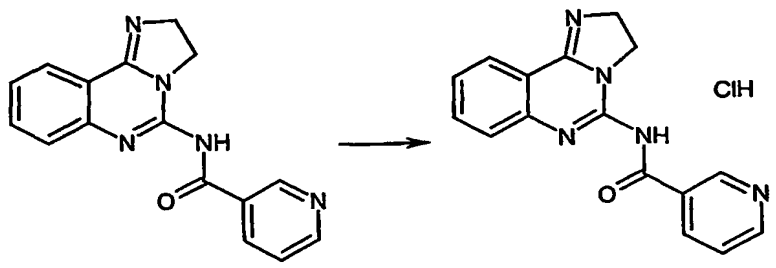
Mass spectrometry: 292 $(M + H)^+$

In vitro activity grade: A

^{1}H-NMR (300 MHz, DMSO-d6): d 4.00 - 4.11 (2H, m), 4.11 - 4.21 (2H, m), 7.29 (1H, ddd, J = 3.0, 5.3, 7.9 Hz), 7.52 (1H, dd, J = 4.9, 7.9 Hz), 7.57 - 7.66 (2H, m), 7.89 (1H, d, J = 7.9 Hz), 8.42 - 8.48 (1H, m), 8.73 (1H, dd, J = 1.9, 4.9 Hz), 9.32 (1H, d, J = 1.1 Hz), 12.36 (1H, s).

Example 2-2:

N-(2,3-Dihydroimidazo[1,2-*c*]quinazolin-5-yl)nicotinamide hydrochloride

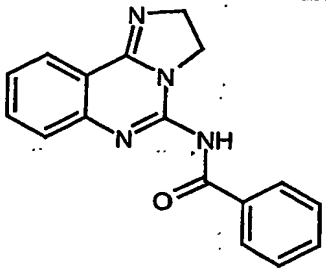
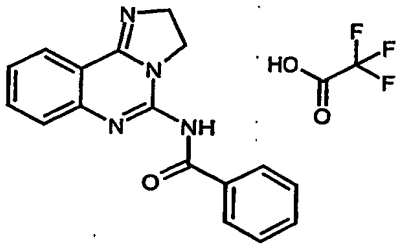
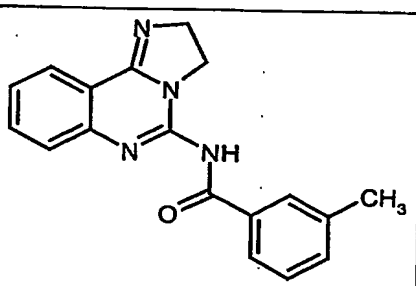
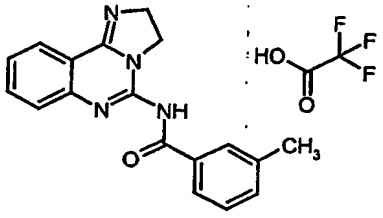


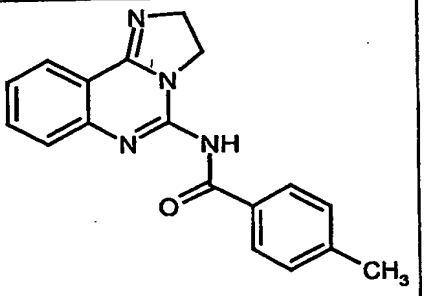
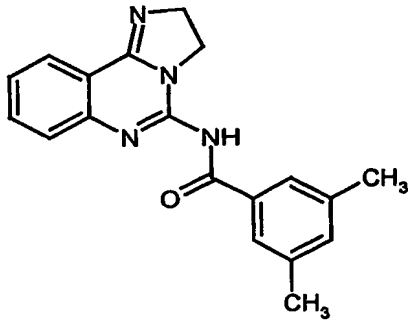
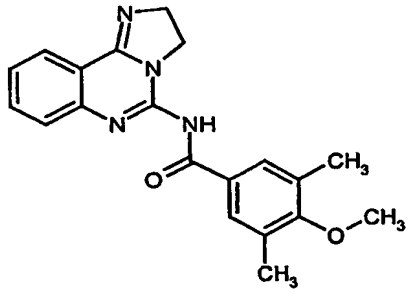
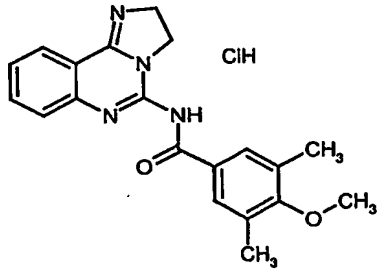
To a suspension of *N*-(2,3-dihydroimidazo[1,2-*c*]quinazolin-5-yl)nicotinamide (150 mg, 0.515 mmol) in tetrahydrofuran (4 ml) at 0°C was added a 4N solution of hydrochloric acid in 1,4-dioxane (2 ml, 8 mmol). The mixture was stirred at room temperature for 1 h, and concentrated under reduced pressure. The resulting residue was trituated with diethyl ether. The resulting precipitate was collected by filtration, washed with ethyl ether, and dried under reduced pressure to give N-(2,3-dihydro-imidazo[1,2-c]quinazolin-5-yl)nicotinamide hydrochloride (192 mg, quantitative).

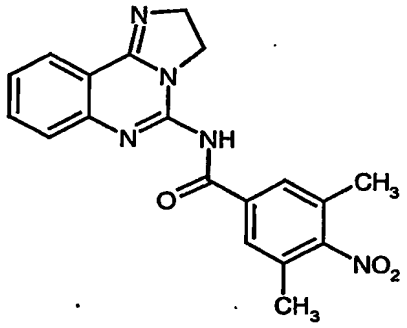
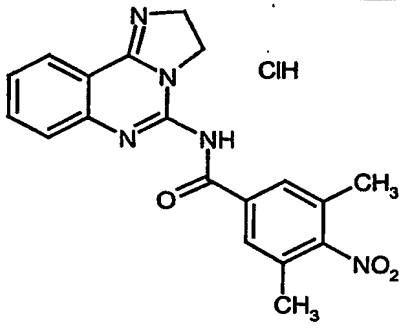
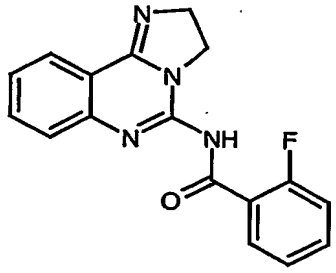
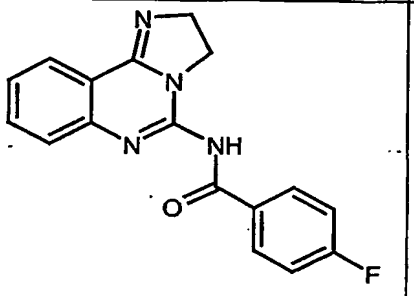
Melting point: 289°C (decomposition)
Molecular weight: 327.78
Mass spectrometry: 292 $(M + H)^+$
In vitro activity grade: A
^{1}H-NMR (300 MHz, DMSO-d6): δ 4.18 - 4.30 (2H, m), 4.54 - 4.65 (2H, m), 7.56 - 7.65 (1H, m), 7.88 (1H, dd, J = 4.9, 7.9 Hz), 7.97 - 8.10 (2H, m), 8.64 (1H, d, J = 7.9 Hz), 8.80 (1H, d, J = 7.9 Hz), 8.95 (1H, dd, J = 1.5, 5.3 Hz), 9.43 (1H, d, J = 1.1 Hz), 12.7 - 13.3 (1H, br).

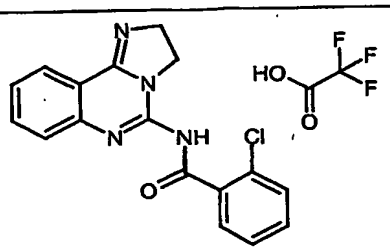
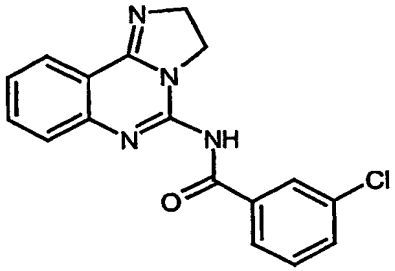
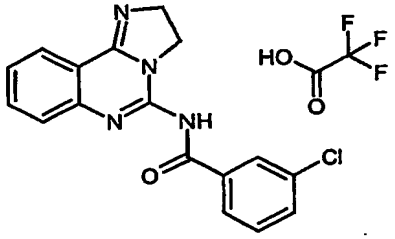
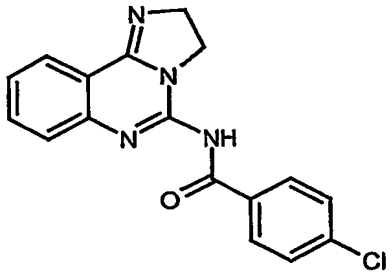
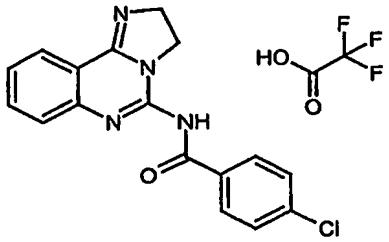
In a similar method according to the Example 2-1 and 2-2 above, the compounds in Example 2-3 to 2-192 were synthesized.

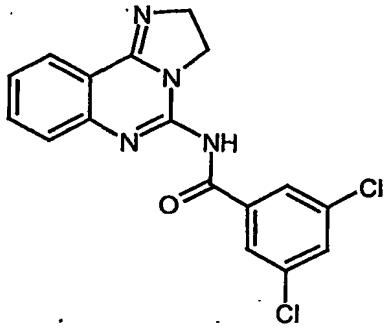
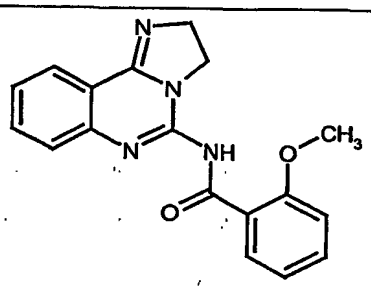
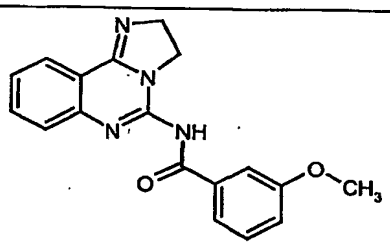
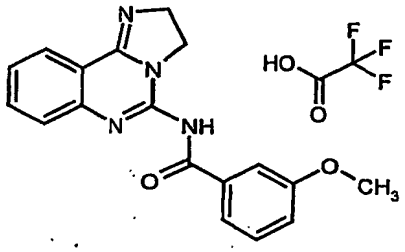
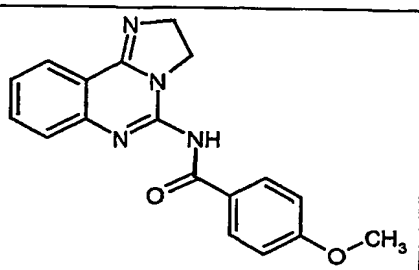
Table 2

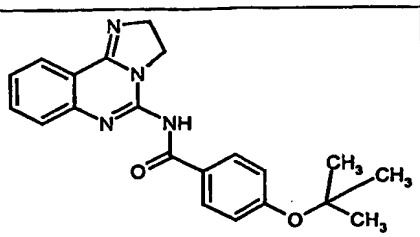
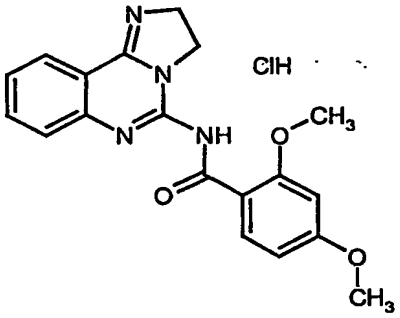
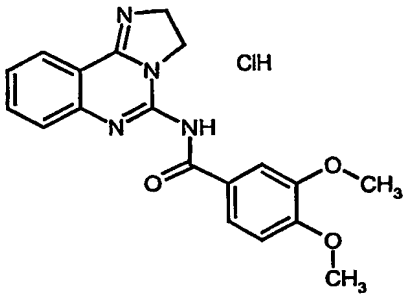
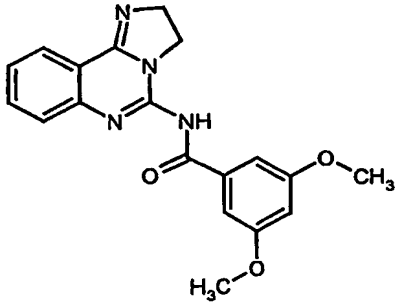
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-3		290,33	291	201-203(dec.)	B
2-4		404,35	291	238-242	A
2-5		304,35	305	201-203	C
2-6		418,38	305	239-241	B

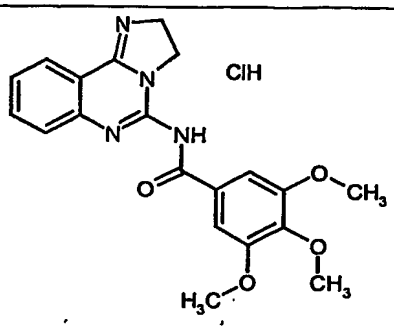
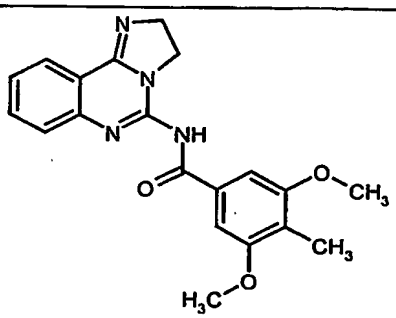
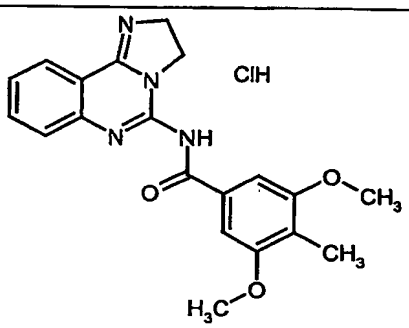
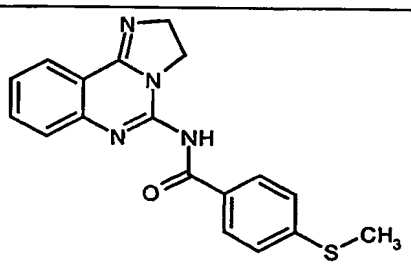
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-7		304,35	305	185-186	C
2-8		318,38	319	246-248	D
2-9		348,41	349	216-218	D
2-10		384,87	349	288 (dec.)	D

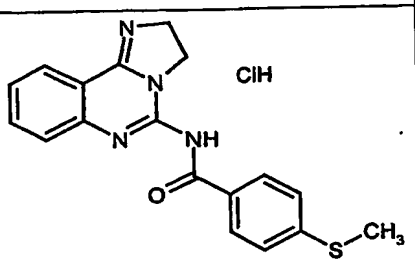
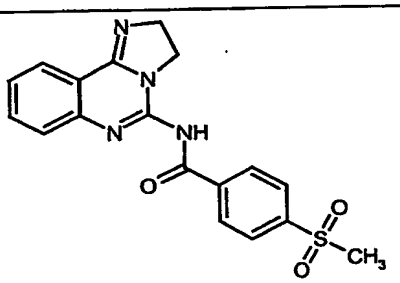
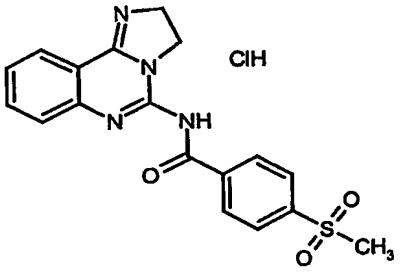
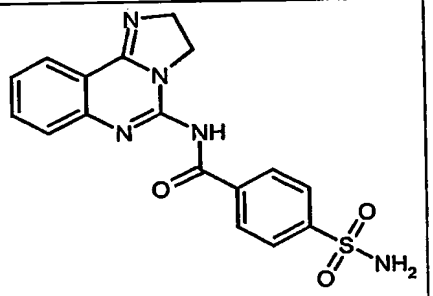
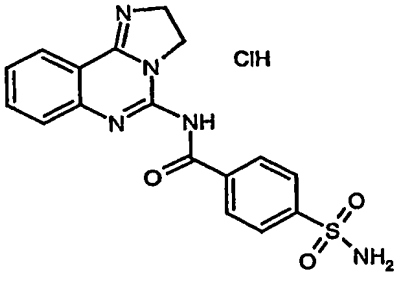
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-11		363,38	364	277 (dec.)	D
2-12		399,84	364	313 (dec.)	D
2-13		308,32	309	202-204	B
2-14		308,32	309	210-212	C

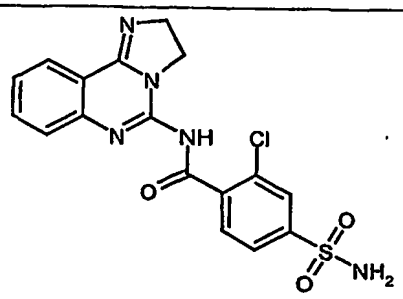
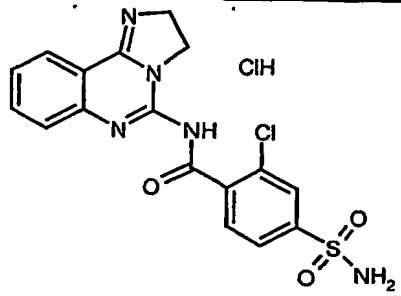
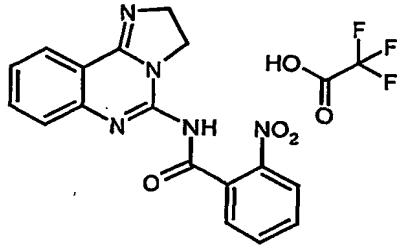
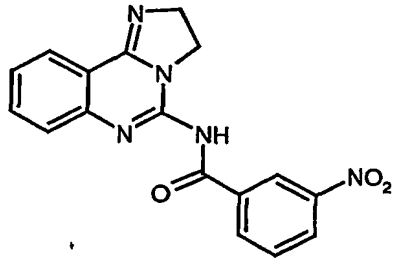
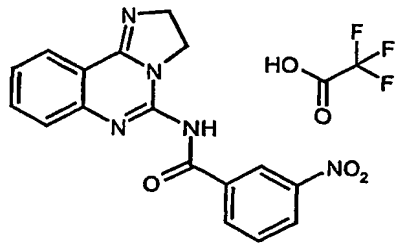
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-15		438,80	325	221-224	C
2-16		324,77	325	196-197	C
2-17		438,80	325	233-235	B
2-18		324,77	325	226-228	D
2-19		438,80	325	243-245	C

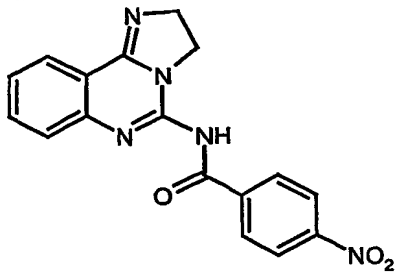
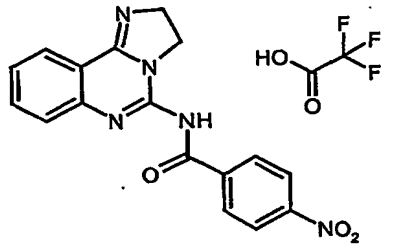
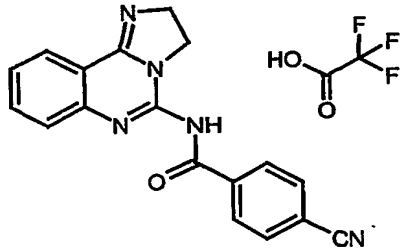
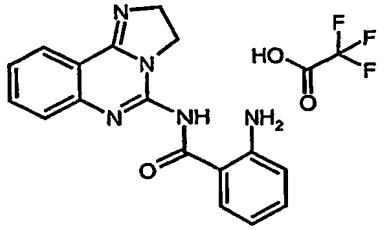
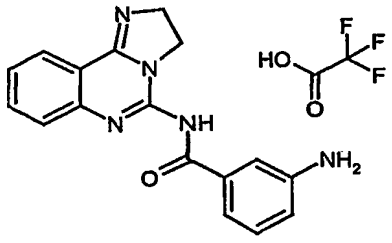
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-20		359,22	358	268-269	D
2-21		320,35	321	185-187	D
2-22		320,35	321	202-204	D
2-23		434,38	321	209-211	B
2-24		320,35	321	300 (dec.)	C

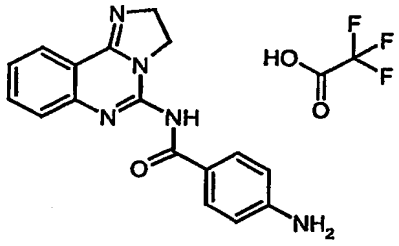
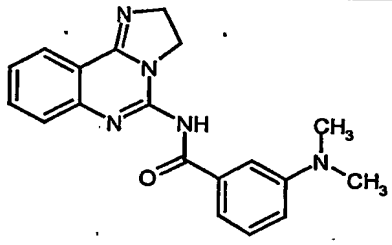
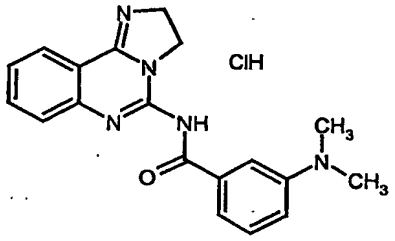
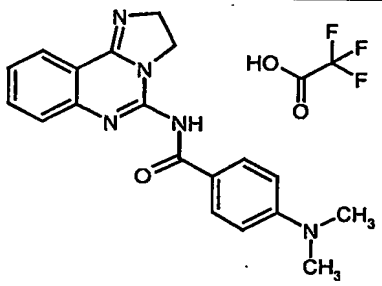
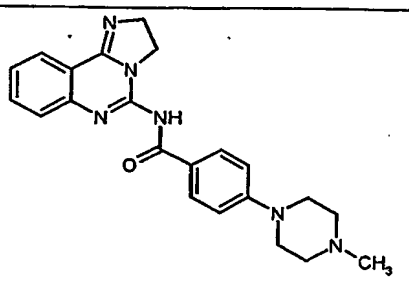
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-25		362,44	363	>410	D
2-26		386,84	351	259 (dec.)	C
2-27		386,84	351	274 (dec.)	A
2-28		350,38	351	330 (dec.)	C

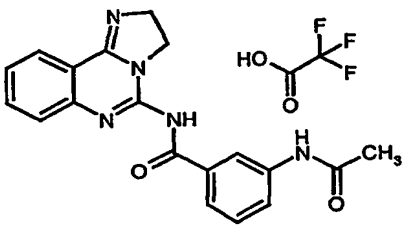
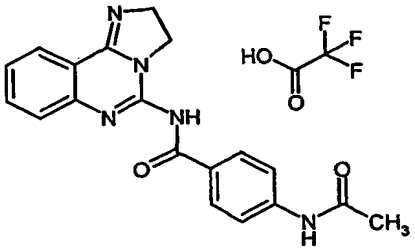
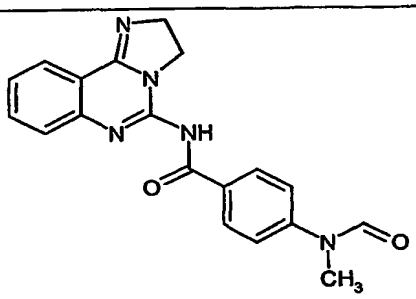
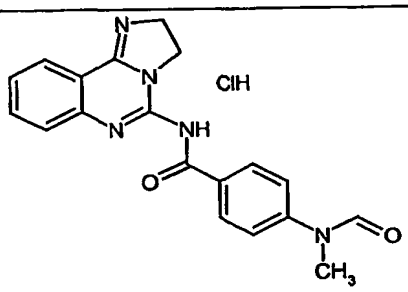
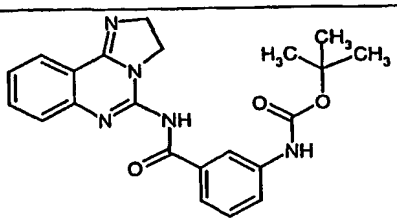
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-29		416,87	381	291 (dec.)	D
2-30		364,41	365	248 (dec.)	D
2-31		400,87	365	321 (dec.)	D
2-32		336,42	337	169-170	C

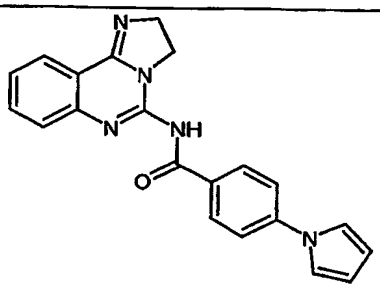
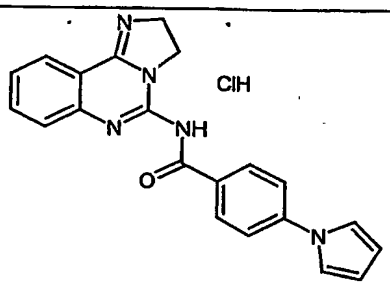
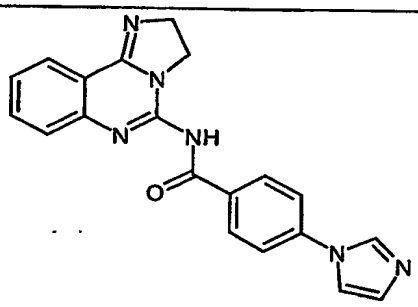
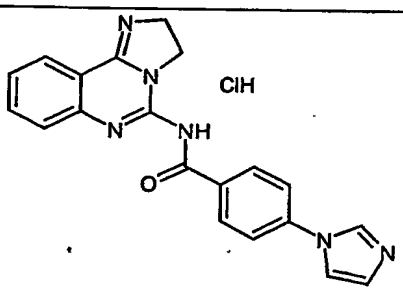
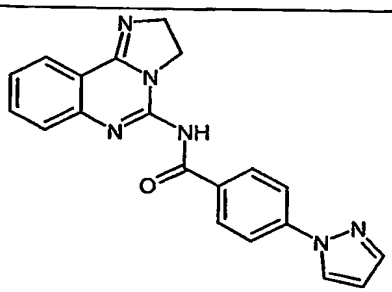
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-33		372,88	337	292 (dec.)	C
2-34		368,42	369	278 (dec.)	D
2-35		404,88	369	320 (dec.)	D
2-36		369,40	370	278 (dec.)	B
2-37		405,87	370	308 (dec.)	B

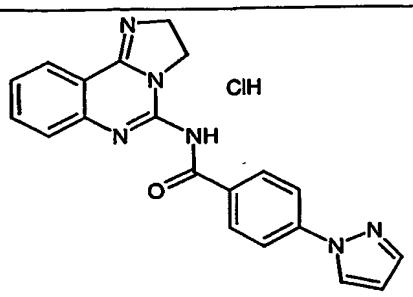
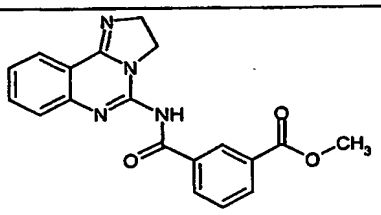
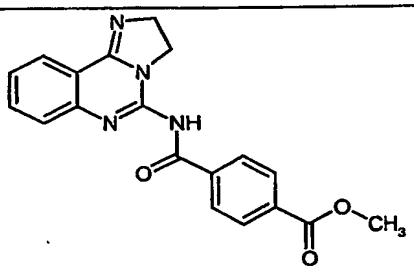
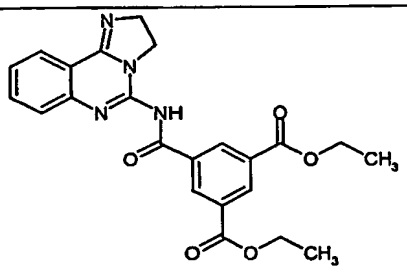
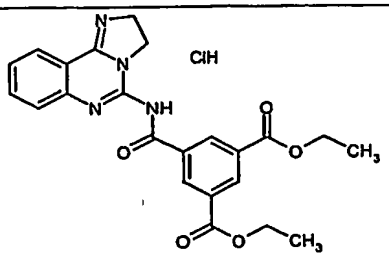
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-38		403,85	403	240 (dec.)	D
2-39		440,31	403	300 (dec.)	D
2-40		449,35	336	198-200	C
2-41		335,32	334	265-267	D
2-42		449,35	336	238-239	C

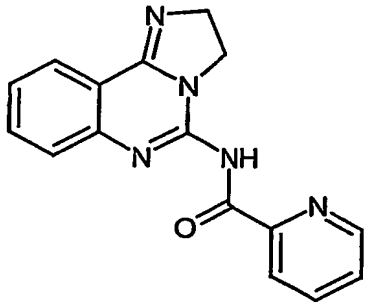
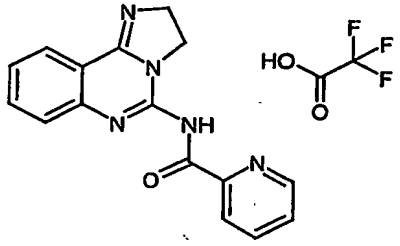
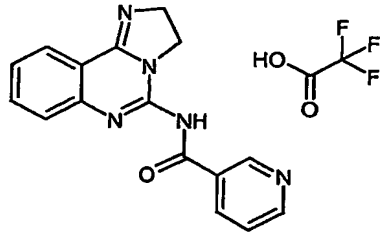
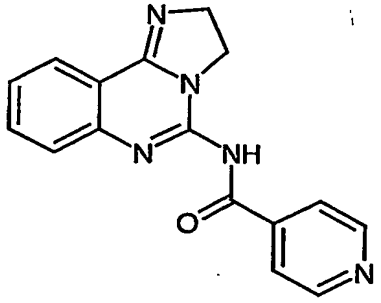
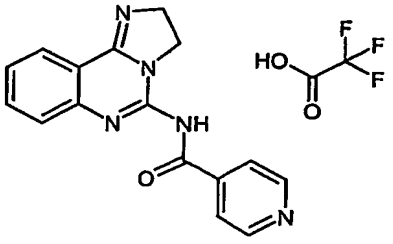
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-43		335,32	334	279-281	D
2-44		449,35	336	265 (dec.)	C
2-45		429,36	316	248-250	C
2-46		419,37	306	175 (dec.)	D
2-47		419,37	306	191 (dec.)	A

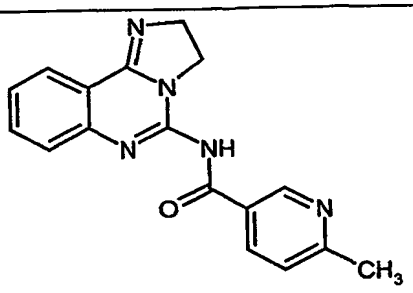
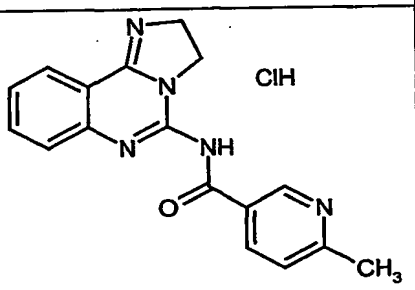
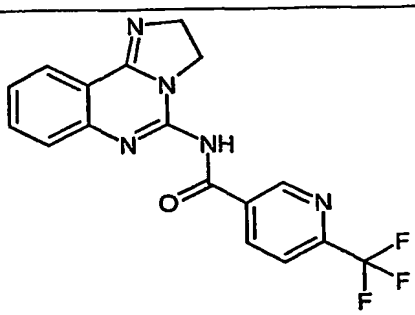
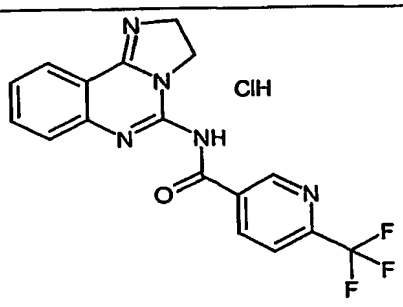
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-48		419,37	306	232 (dec.)	A
2-49		333,40	334	188-190	C
2-50		369,86	334	266 (dec.)	C
2-51		447,42	334	240 (dec.)	C
2-52		388,48	389	218-222	D

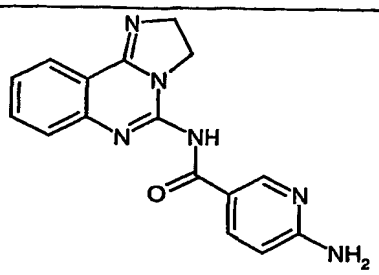
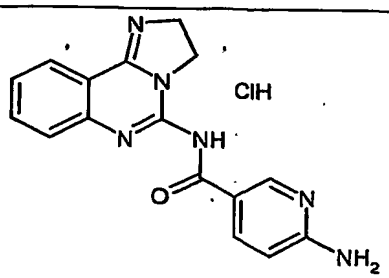
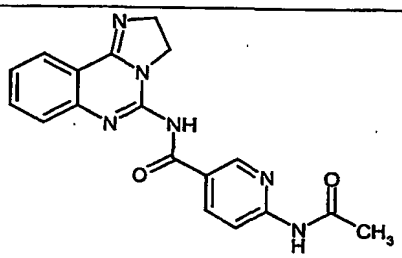
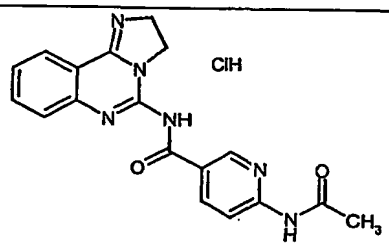
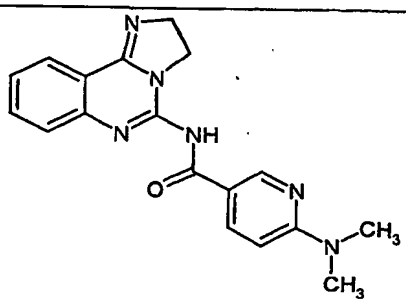
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-53		461,40	348	253 (dec.)	C
2-54		461,40	348	247 (dec.)	A
2-55		347,38	348	208-210	D
2-56		383,84	348	304 (dec.)	D
2-57		405,46	406	280 (dec.)	D

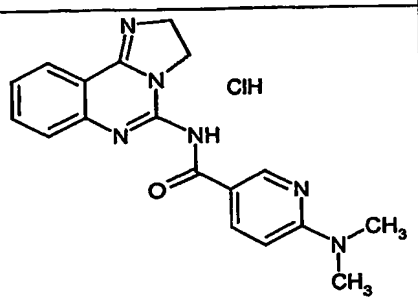
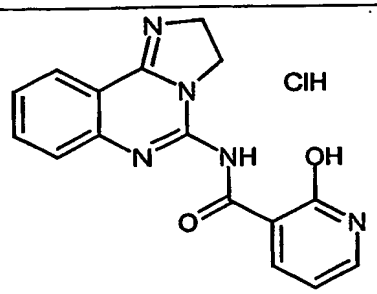
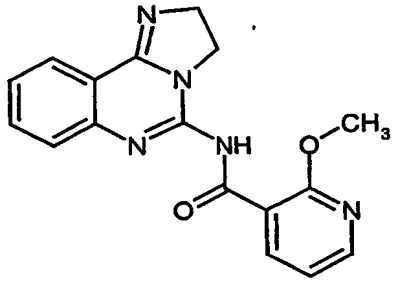
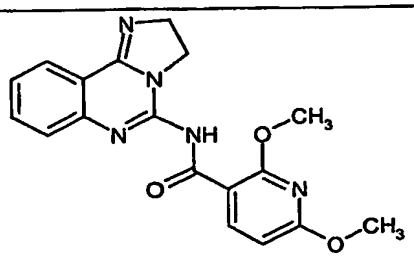
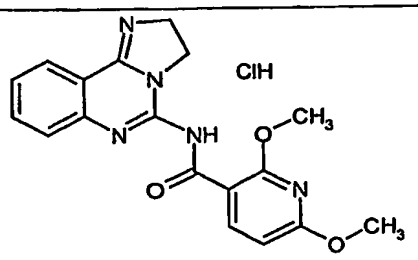
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-58		355,40	356	218-220	D
2-59		391,86	356	309 (dec.)	D
2-60		356,39	357	267 (dec.)	D
2-61		392,85	357	324 (dec.)	D
2-62		356,39	357	209-211	D

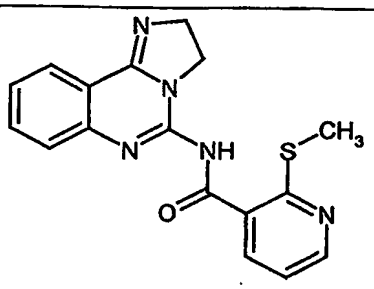
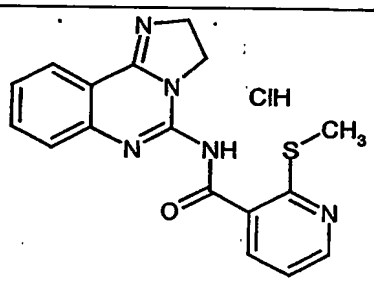
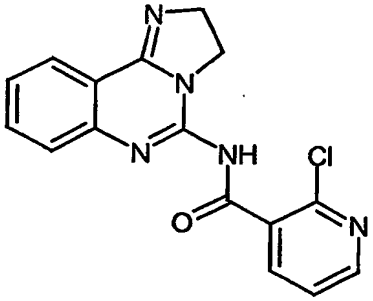
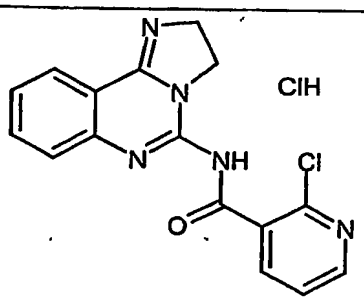
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-63		392,85	357	319 (dec.)	D
2-64		348,36	349	224-226	D
2-65		348,36	349	253-255	D
2-66		434,46	435	289 (dec.)	D
2-67		470,92	435	282	D

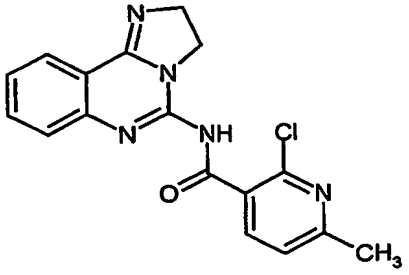
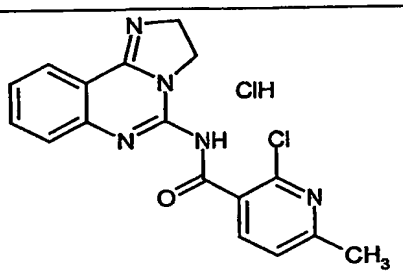
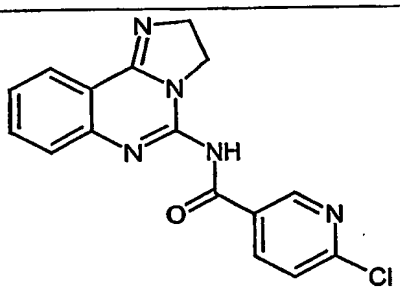
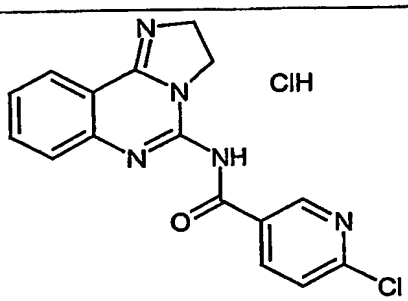
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-68		291,31	292	204 - 205	B
2-69		405,34	292	206 (dec.)	B
2-70		405,34	292	237-239	A
2-71		291,31	292	224 - 225	B
2-72		405,34	292	2310(dec.)	B

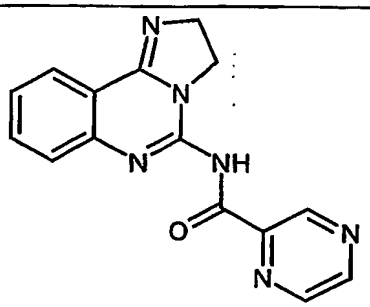
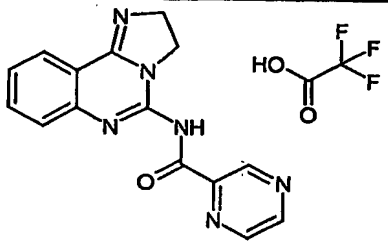
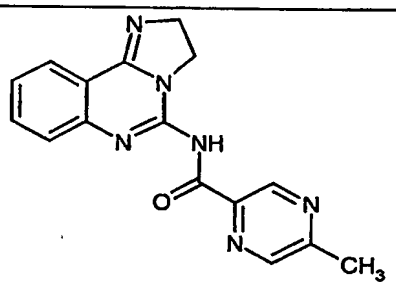
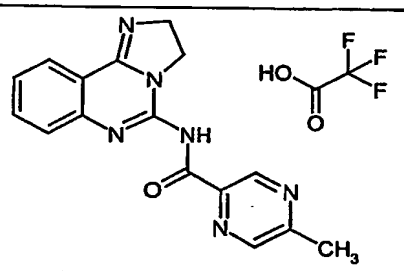
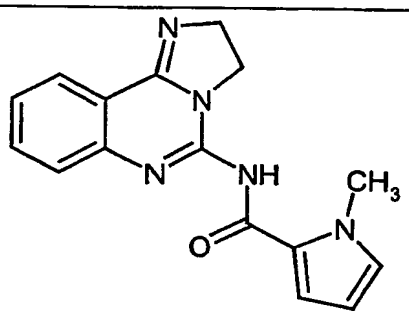
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-73		305,34	306	195 - 196	A
2-74		341,80	306	310 (dec.)	A
2-75		359,31	360	219 - 220	D
2-76		395,77	360	> 250	B

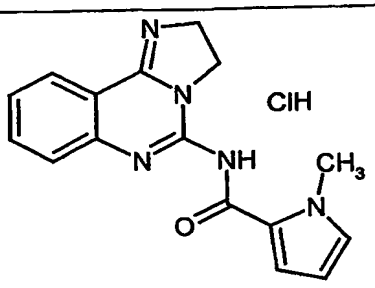
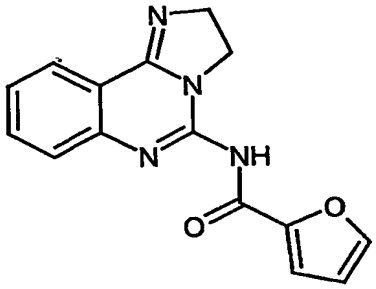
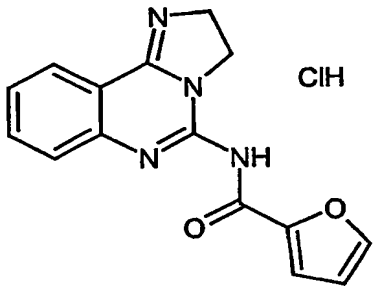
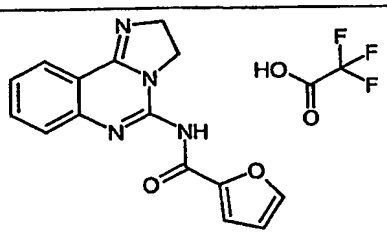
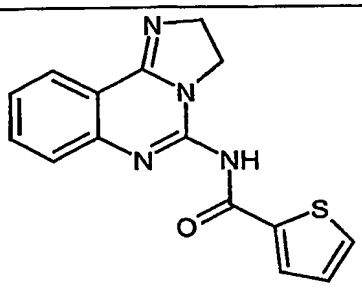
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-77		306,33	307	> 300	A
2-78		342,79	307	290 (dec.)	A
2-79		348,37	349	320 (dec.)	A
2-80		384,83	349	312 (dec.)	A
2-81		334,38	335	249 (dec.)	C

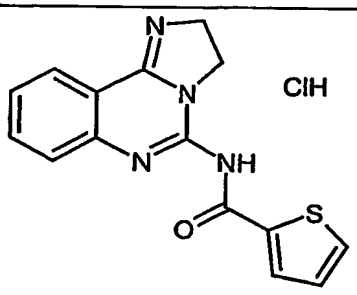
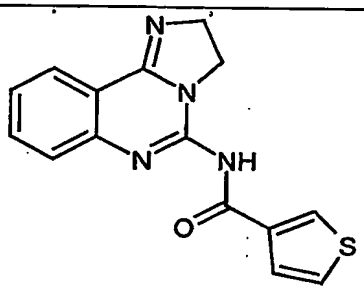
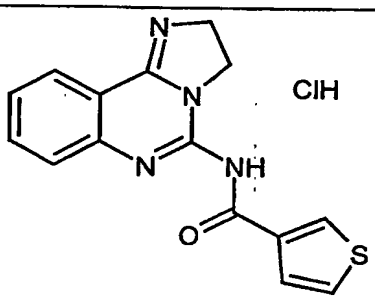
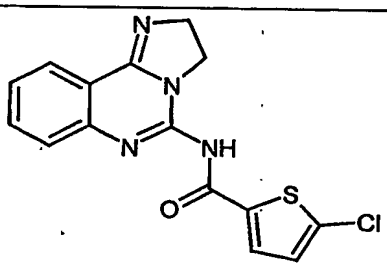
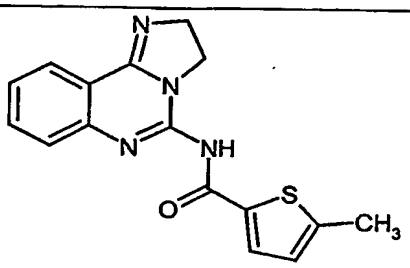
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-82		370,84	335	311 (dec.)	B
2-83		343,78	308	346 (dec.)	C
2-84		321,34	322	198 - 199	B
2-85		351,37	352	244 - 245	D
2-86		387,83	352	210 (dec.)	B

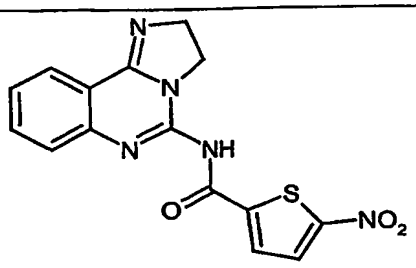
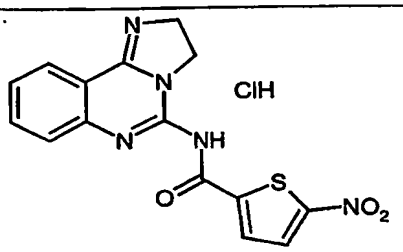
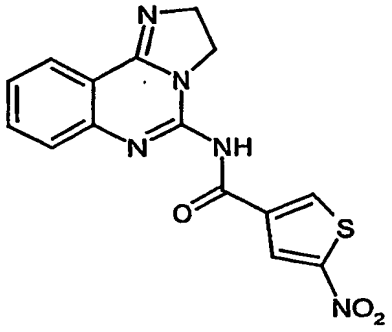
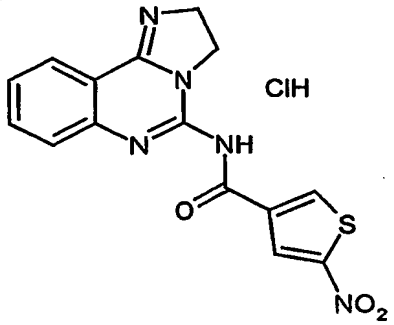
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-87		337,41	338	233 - 234	C
2-88		373,87	338	298 - 299	B
2-89		325,76	326	198 - 199	A
2-90		362,22	326	340 (dec.)	A

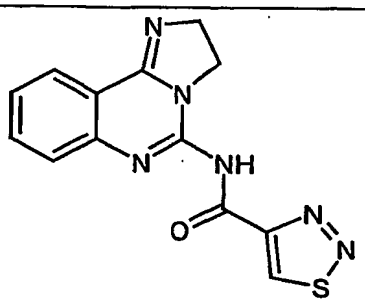
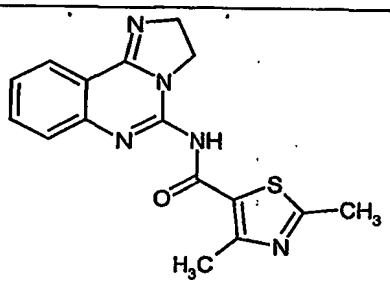
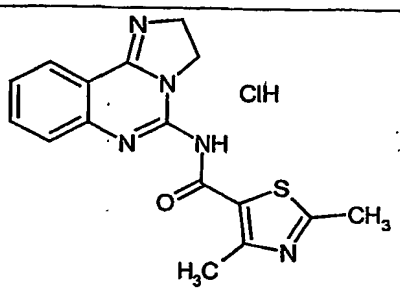
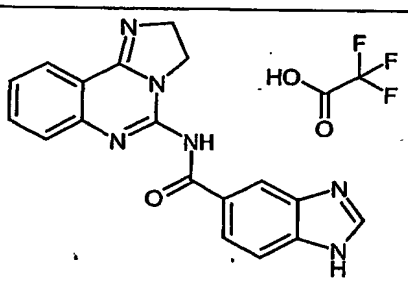
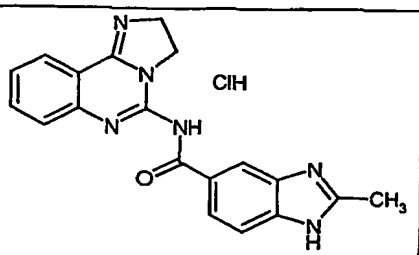
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-91		339,79	340	213 - 214	A
2-92		376,25	340	287 (dec.)	A
2-93		325,76	326	246 - 247	A
2-94		362,22	326	324 (dec.)	A

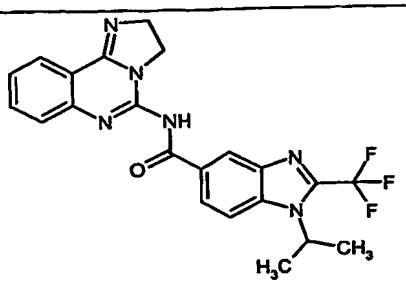
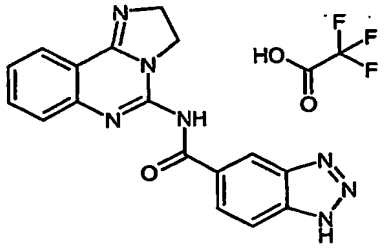
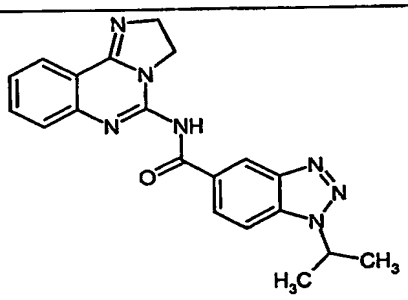
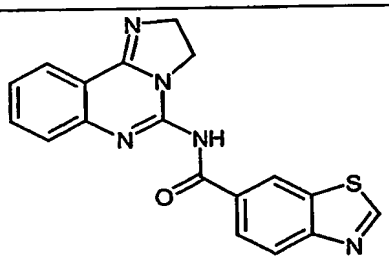
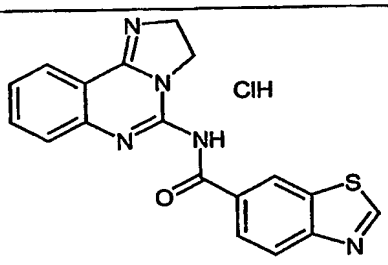
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-95		292,30	293	267 - 268	B
2-96		406,33	293	234 (dec.)	B
2-97		306,33	307	257 (dec.)	B
2-98		420,35	307	231 (dec.)	B
2-99		293,33	294	128 - 129	B

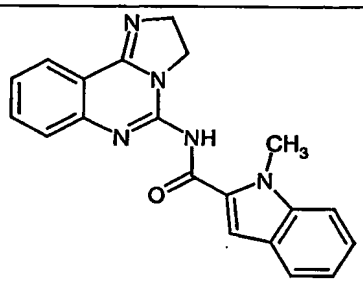
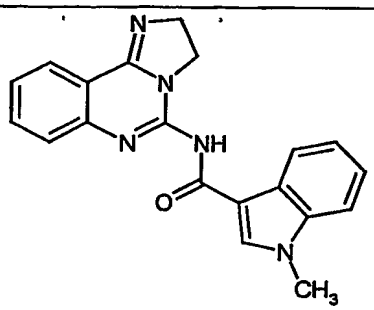
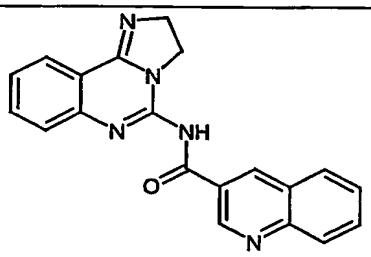
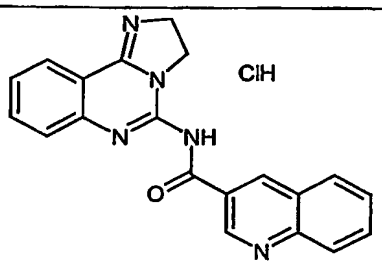
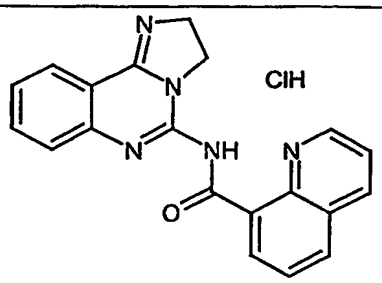
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-100		329,79	294	264 (dec.)	B
2-101		280,29	281	350 (dec.)	B
2-102		316,75	281	311 (dec.)	B
2-103		394,31	281	230-232	A
2-104		296,35	297	187 - 188	A

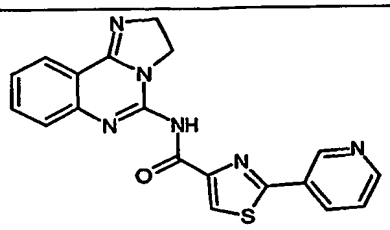
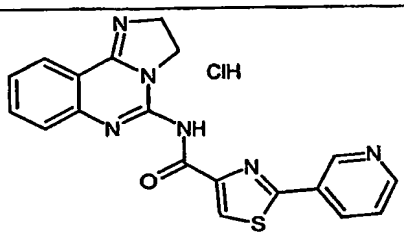
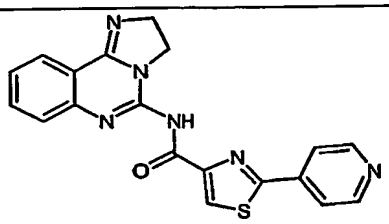
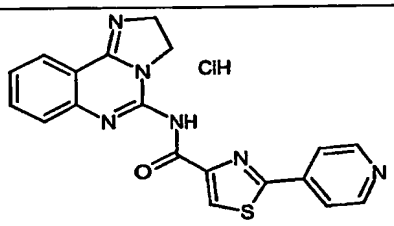
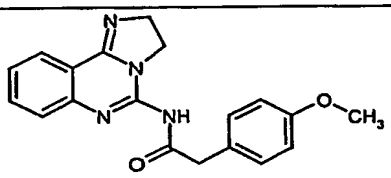
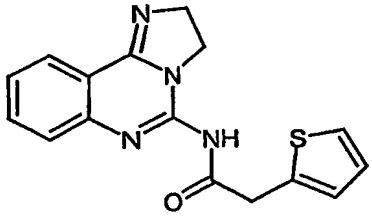
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-105		332,81	297	310 (dec.)	A
2-106		296,35	297	167 (dec.)	A
2-107		332,81	297	297 (dec.)	A
2-108		330,80	331	198 (dec.)	D
2-109		310,38	311	192 - 193	B

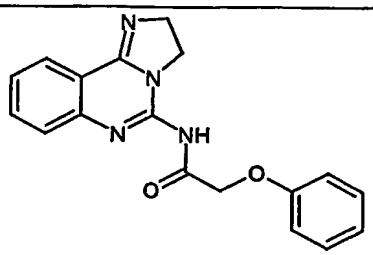
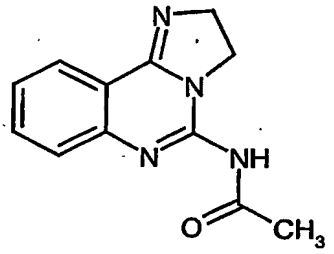
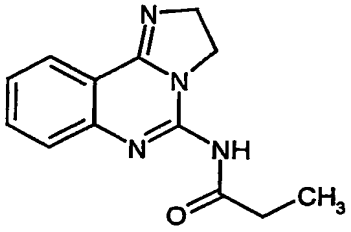
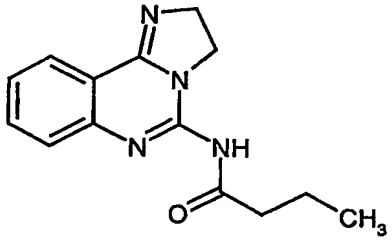
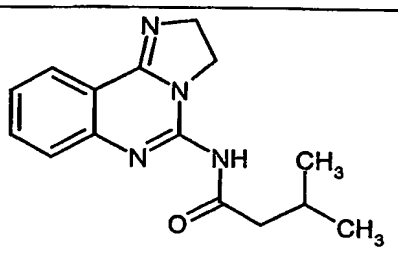
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-110		341,35	342	286 - 287	D
2-111		377,81	342	300 (dec.)	D
2-112		341,35	342	269 - 270	D
2-113		377,81	342	296 (dec.)	D

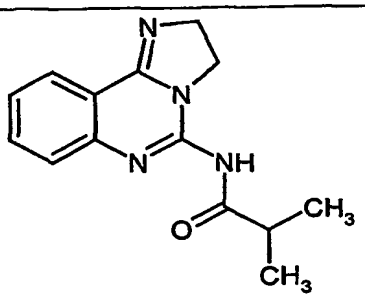
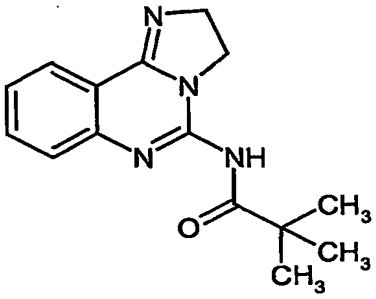
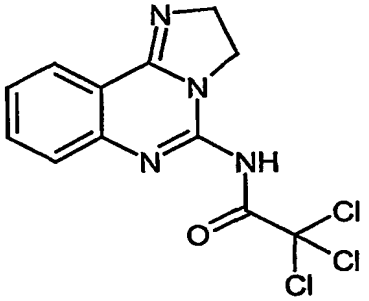
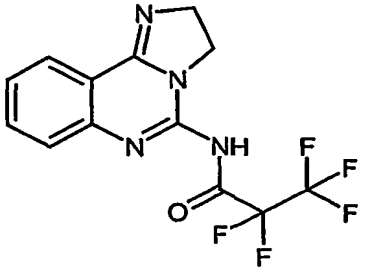
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-114		298,33	299	219 (dec.)	B
2-115		325,39	326	243 (dec.)	A
2-116		361,86	326	289 - 290	A
2-117		444,38	331	221 (dec.)	A
2-118		380,84	345	344 (dec.)	A

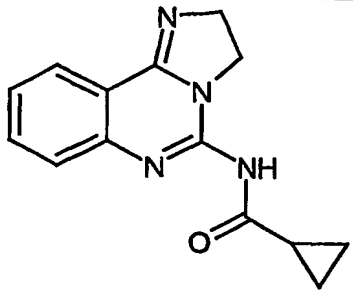
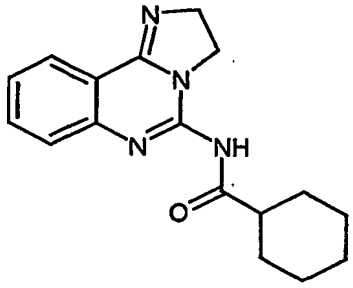
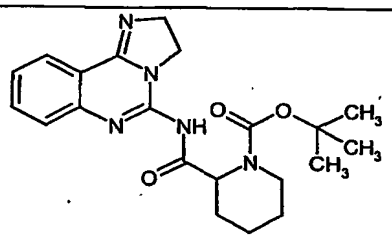
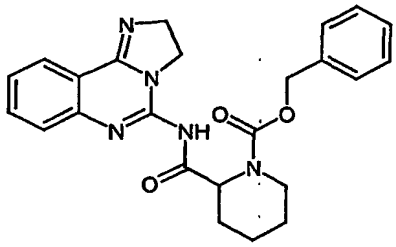
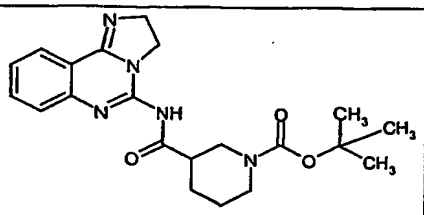
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-119		440,43	441	250-253	D
2-120		445,36	332	252 (dec.)	A
2-121		373,42	374	202-203	D
2-122		347,40	348	303-305	D
2-123		383,86	348	314 (dec.)	B

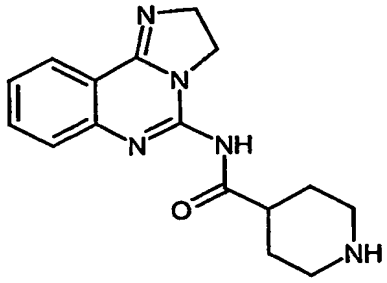
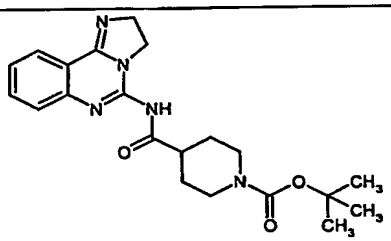
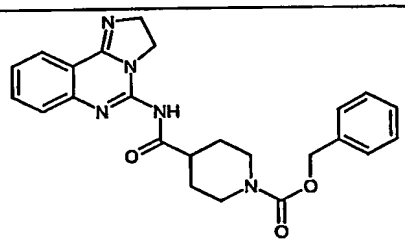
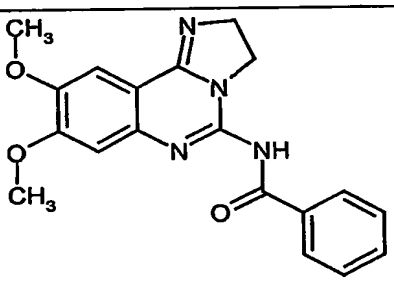
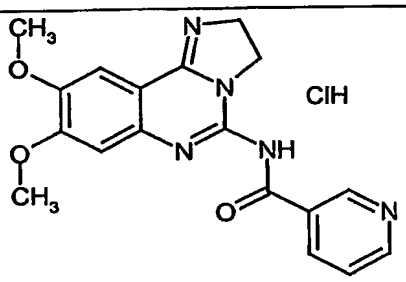
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-124		343,39	344	259 - 260	D
2-125		343,39	344	288 - 289	D
2-126		341,38	342	263 - 264	C
2-127		377,84	342	319 (dec.)	A
2-128		377,84	342	316 (dec.)	D

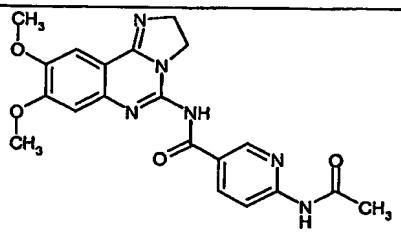
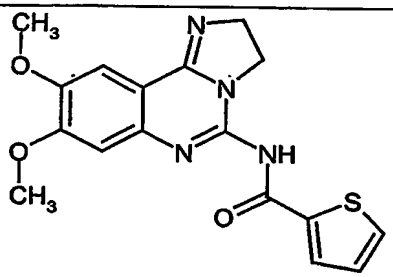
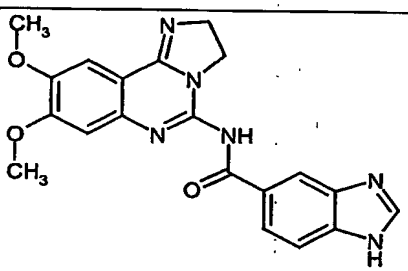
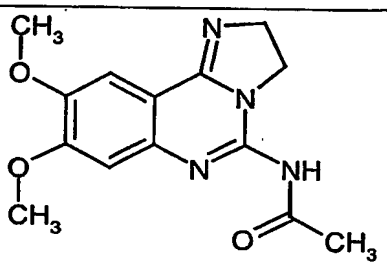
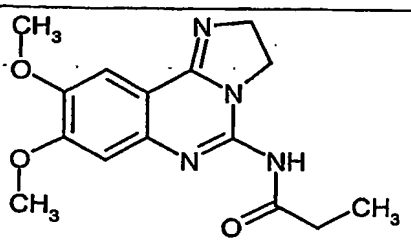
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-129		374,43	375	260 - 261	D
2-130		410,89	375	310 (dec.)	D
2-131		374,43	375	281 (dec.)	D
2-132		410,89	375	335 (dec.)	D
2-133		334,38	335	167 - 168	D
2-134		310,38	311	122 - 123	C

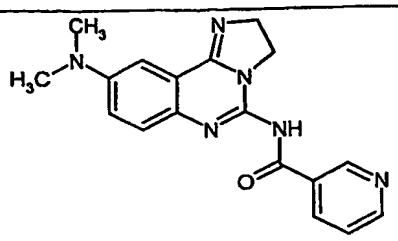
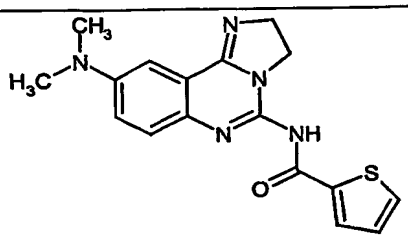
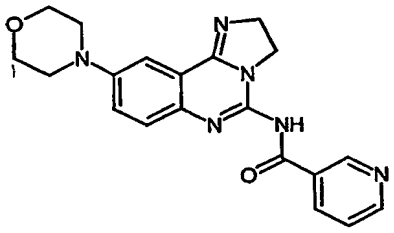
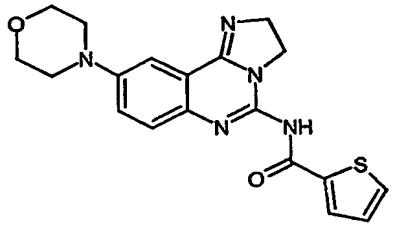
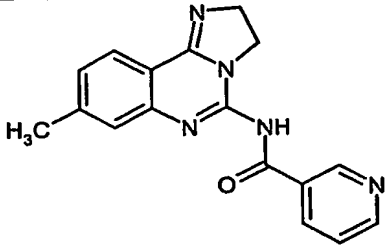
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-135		320,35	321	149 - 150	D
2-136		228,26	229	189	D
2-137		242,28	243	amorphous	D
2-138		256,31	257	121-122	D
2-139		270,34	271	154 (dec.)	D

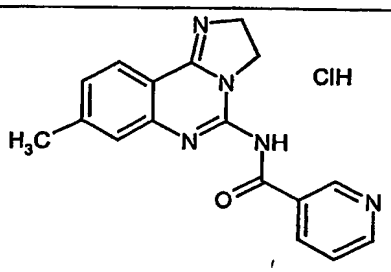
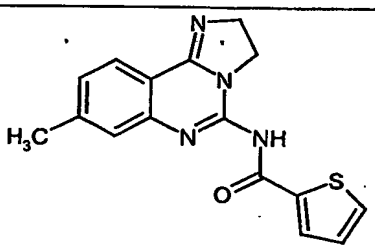
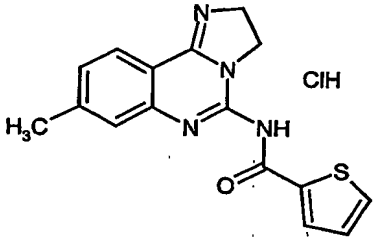
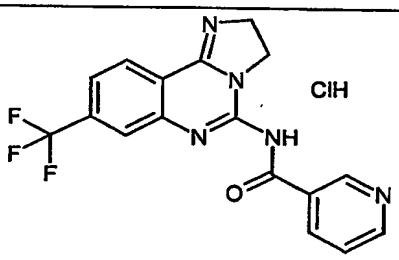
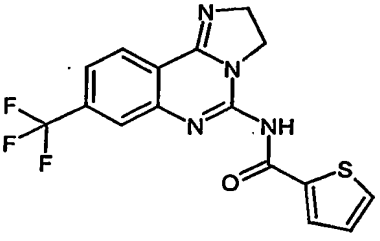
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-140		256,31	257	104-105	D
2-141		270,34	271	135-136	C
2-142		331,59	331	194 (dec.)	B
2-143		332,23	333	210-211	C

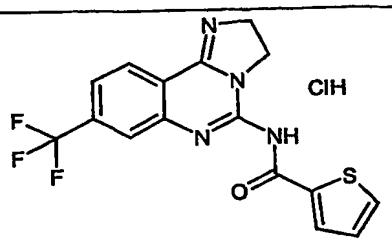
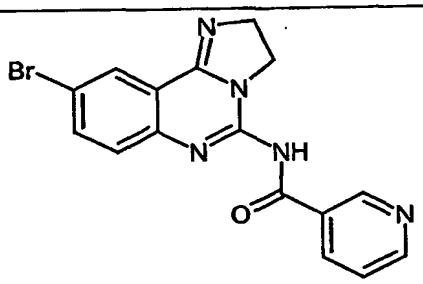
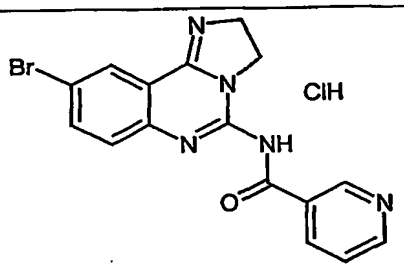
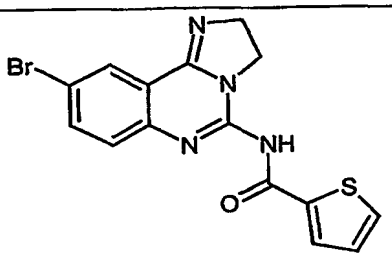
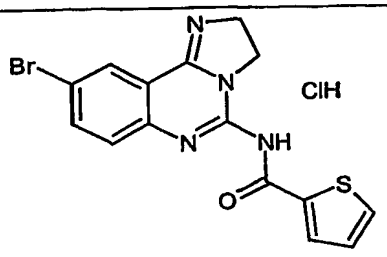
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-144		254,29	255	164 - 165	C
2-145		296,38	297	170-172	D
2-146		397,48	398	amorphous	D
2-147		431,50	432	119 - 120	D
2-148		397,48	398	147 - 148	C

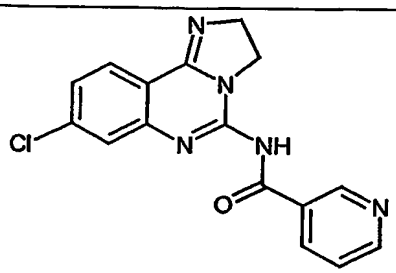
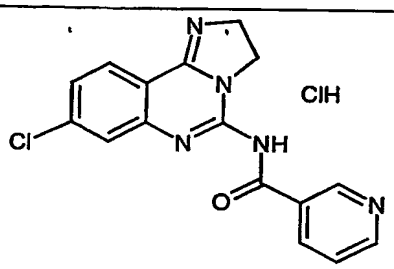
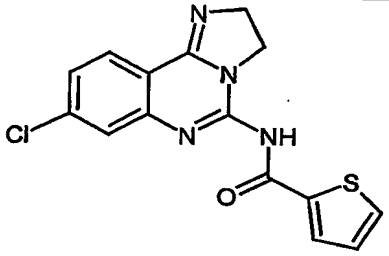
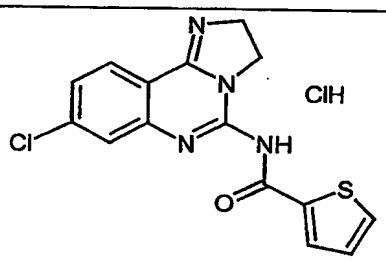
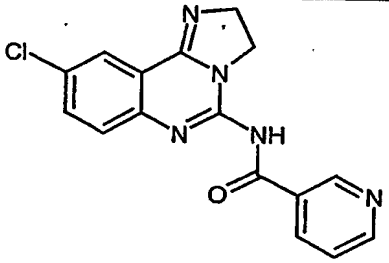
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-149		297,36	298	179 - 180	D
2-150		397,48	398	amorphous	D
2-151		431,50	432	111 - 112	D
2-152		350,38	351	amorphous	B
2-153		387,83	352	246	A

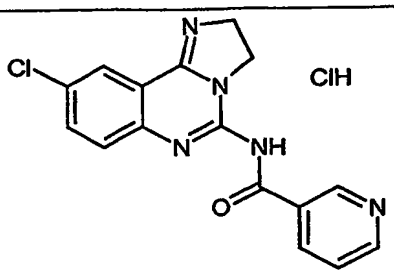
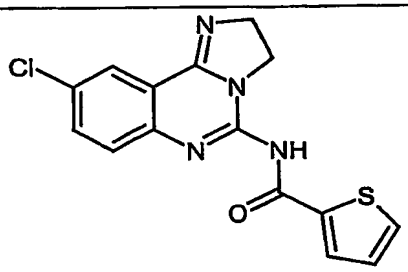
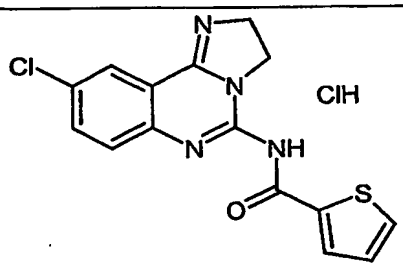
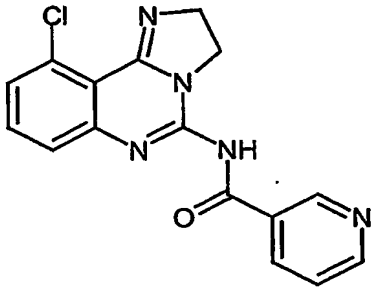
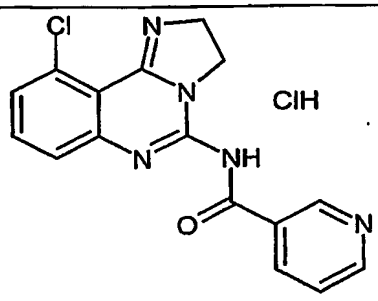
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-154		408,42	409	294	A
2-155		356,41	357	248	A
2-156		390,40	391	246	A
2-157		288,31	289	240-241	D
2-158		302,34	303	224-225	D

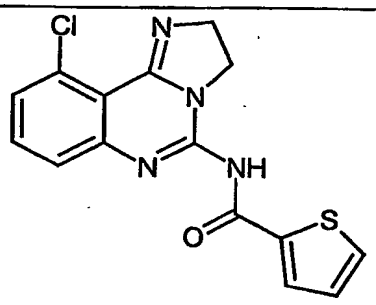
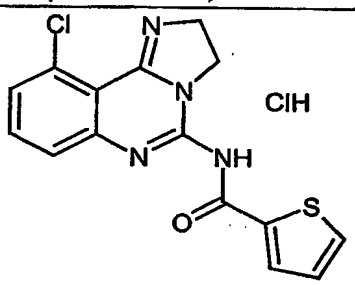
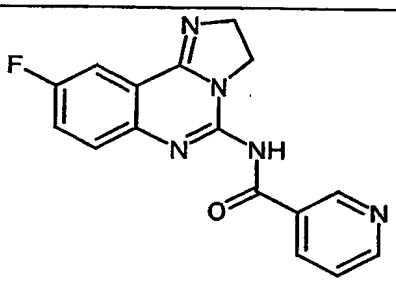
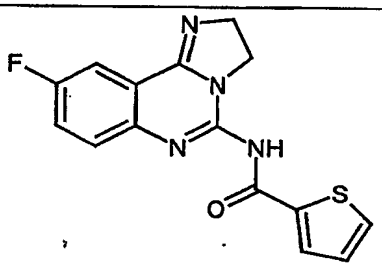
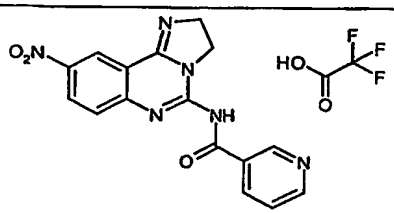
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-159		334,38	335	269	B
2-160		339,42	340	272	C
2-161		376,42	377	244	C
2-162		381,46	382	124	C
2-163		305,34	306	207	A

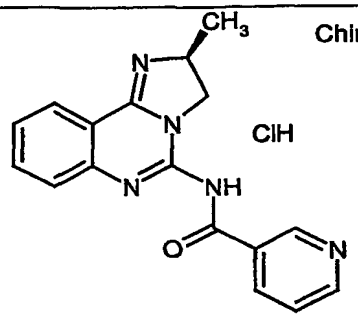
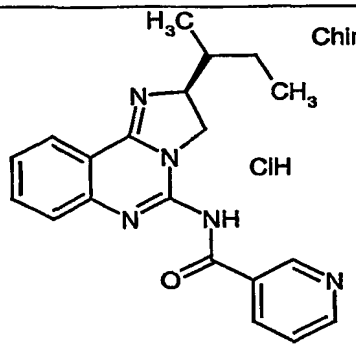
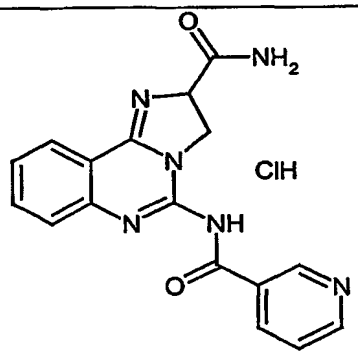
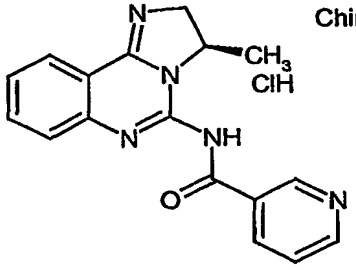
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-164		341,80	306	315	A
2-165		310,38	311	182	A
2-166		346,84	311	276	A
2-167		395,77	360	275	A
2-168		364,35	365	226	A

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-169		400,81	365	292	B
2-170		370,21	371	228	A
2-171		406,67	371	316	A
2-172		375,25	376	232	C
2-173		411,71	376	275	B

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-174		325,76	326	254	A
2-175		362,22	326	308	A
2-176		330,80	331	228	B
2-177		367,26	331	328	A
2-178		325,76	326	210	A

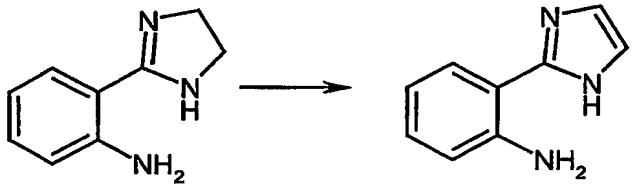
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-179		362,22	326	309	A
2-180		330,80	331	174	B
2-181		367,26	331	276	A
2-182		325,76	326	243	B
2-183		362,22	326	249	A

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-184		330,80	331	233	D
2-185		367,26	331	227	B
2-186		309,31	310	242	B
2-187		314,34	214	315	B
2-188		450,34	336	224	B

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
2-189		341,80	306	204(dec.)	D
2-190		383,88	348	230-240	D
2-191		370,80	335	274(dec.)	D
2-192		341,80	306	270(dec.)	C

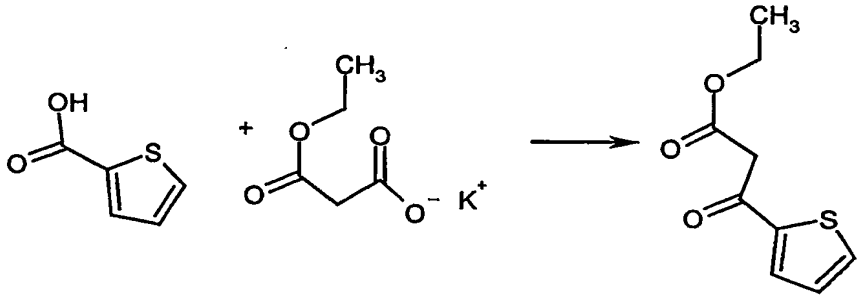
Example 3-1

(1) 2-(*1H*-Imidazol-2-yl)aniline



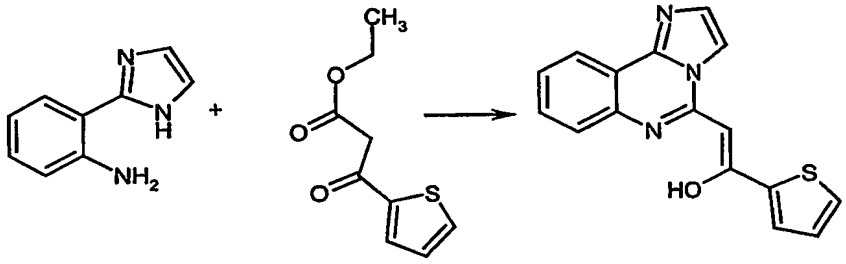
A mixture of 2-(4,5-dihydro-*1H*-imidazol-2-yl)aniline hydrobromide (50.0 mg, 0.207 mmol) and manganese dioxide (170 mg, 1.96 mmol) in *N,N'*-dimethylpropylenurea (2.0 mL) was heated at 150. (bath temp.). After 1 hour, the reaction mixture was cooled to room temperature, poured into a solution of hydroxylamine hydrochloride (0.5 g) in water (50 mL), and the resulting mixture was extracted with ethyl acetate. The separated organic layer was washed with brine, dried over magnesium sulfate, filtered, concentrated under reduced pressure. The crude residue was triturated with isopropylether, and the precipitate was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by preparative thin layer chromatography (silica-gel, ethyl acetate as the eluent) to give 2-(1H-imidazol-2-yl)aniline (20 mg, 61% yield).

(2) Ethyl 3-oxo-3-(2-thienyl)propanoate



To a suspension of 2-thiophenecarboxylic acid (6.48 g, 50.57 mmol) in tetrahydrofurane (100 ml) at 5. was added 1,1'-Carbonyldiimidazole (8.61 g, 53.09 mmol) by portions. The mixture was allowed to warm to room temperature, and the stirring was continued for 1 hour. The reaction mixture was added into a suspension mixture of magnesium chloride (4.86 g, 51.07 mmol) and pottasium 3-ethoxy-3-oxopropanoate (12.91 g, 75.85 mmol) in tetrahydrofurane (50 ml). After being stirred at 50. for 2 hours and at room temperature overnight, the reaction mixture was poured into water ,and then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel (ethyl acetate/ hexane, 15/85) to give ethyl 3-oxo-3-(2-thienyl)propanoate (7.83 g, 78% yield) as a yellow oil.

(3) (*Z*)-2-Imidazo[1,2-c]quinazolin-5-yl-1-(2-thienyl)ethenol



A mixture of 2-(1*H*-imidazol-2-yl)aniline (60.0 mg, 0.38 mmol), ethyl3-oxo-3-(2-thienyl)propanoate (74.7 mg, 0.38 mmol) and p-tolenesulfonicacid monohydrate (36.1 mg, 0.19 mmol) in toluene (30 ml) was heated at reflux for 2 hours. After cooling to room temperature, the reaction mixture was poured into aqueous saturate $NaHCO_3$ solution, and the resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel (ethyl acetate/

hexane, 2/3 - 1/1) to give (*Z*)-2-imidazo[1,2-*c*]quinazolin-5-yl-1-(2-thienyl)ethenol (37.0 mg, 33% yeild) as a yellow powder.

Melting point: 128°C

Molecular weight: 293.35

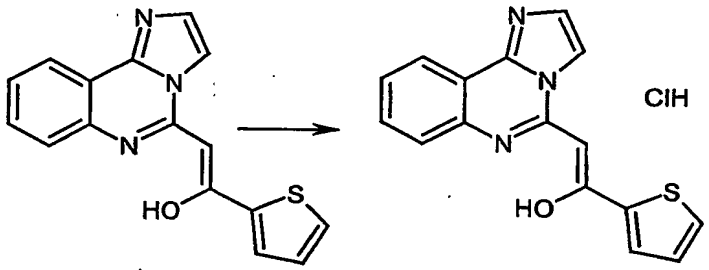
Mass spectrometry: 294 $(M + H)^+$

In vitro activity grade: D

^{1}H-NMR (300 MHz, CDCl3): d 6.11 (1H, s), 7.16 (1H, dd, J = 3.8, 4.9 Hz), 7.34 - 7.41 (2H, m), 7.53 - 7.60 (3H, m), 7.64 (1H, d, J = 1.7 Hz), 7.73 (1H, dd, J = 1.1, 3.8 Hz), 8.34 (1H, dd, J = 0.9, 7.8 Hz), 14.70 (1H, bs).

Example 3-2

(*Z*)-2-Imidazo[1,2-*c*]quinazolin-5-yl-1-(2-thienyl)ethenol hydrochloride



To a solution of (*Z*)-2-imidazo[1,2-*c*]quinazolin-5-yl-1-(2-thienyl)ethenol (0.06 g, 0.07 mmol) in chloroform (1.0 ml) was added a 4N solution of HCl in 1,4-dioxane (0.5 ml). The mixture was diluted with ethyl ether, and the resulting precipitate was collected by filtration, washed with ethyl ether, and dried under reduced pressure to give (*Z*)-2-imidazo[1,2-*c*]quinazolin-5-yl-1-(2-thienyl)ethenol hydrochloride (0.07 g, quantative) as a yellow solid.

Melting point: 263°C (decomposition)

Molecular weight: 329.81

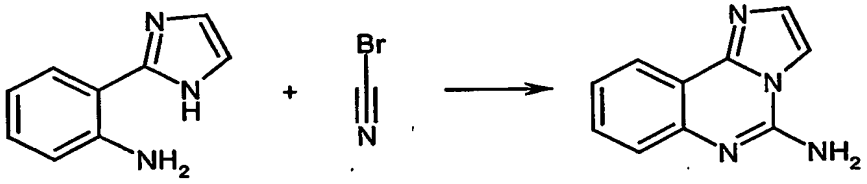
Mass spectrometry: 294 $(M + H)^+$

In vitro activity grade: D

^{1}H-NMR (300 MHz, DMSO-d6): δ 6.79 (1H, s), 7.28 (1H, dd, J = 3.8, 4.9 Hz), 7.45 (1H, t, J = 7.0 Hz), 7.66 - 7.77 (2H, m), 7.82 (1H, d, 1.7), 7.91 (1H, dd, J = 1.1, 5.0 Hz), 8.17 (1H, dd, J = 1.1, 3.8 Hz), 8.30 (1H, dd, J = 1.0, 8.0 Hz), 8.62 (1H, d, J = 1.7 Hz), 14.36 (1H, br).

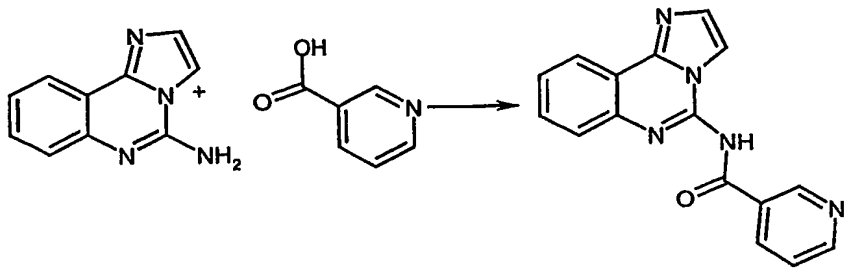
Example 4-1

(1) Imidazo[1,2-c]quinazolin-5-amine



To a solution of 2-(1*H*-imidazol-2-yl)aniline (0.06 g. 0.38 mmol) in methanol (3 ml) was added cyanogen bromide (0.05 g, 0.45 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was poured into water, and the resulting precipitate was collected by filtration, washed with acetone, and dried under reduced pressure to give imidazo[1,2-*c*]quinazolin-5-amine hydrobromide (0.06 g, 61% yield) as a white solid.

(2) *N*-Imidazo[1,2-*c*]quinazolin-5-ylnicotinamide



To a mixture of imidazo[1,2-*c*]quinazolin-5-amine hydrobromide (93 mg, 0.35 mmol) and nicotinic acid (124 mg, 1.01 mmol) and DMF (2.5 ml) at room temperature was added benzotriazole-l-yl-oxy-tris-pyrrolidino-

phosphonium hexaflurrophosphate (525 mg, 1.01 mmol) followed by *N,N*-diisopropylethyl amine (0.264 ml, 1.51 mmol), and the mixture was stirred at 80 . for 6 hours. After cooling to room temperature, the reaction mixture was poured into aqueous saturated $NaHCO_3$ solution. The resulting precipitate was collected by filtration, washed with acetone, and dried under reduced pressure to give *N*-imidazo[1,2-c]quinazolin-5-ylnicotinamide (40 mg, 39% yield) as a white solid.

Melting point: 223-224 °C (decomposition)

Molecular weight: 289.30

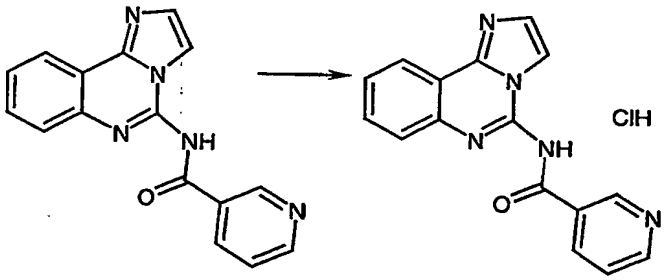
Mass spectrometry: 290 $(M + H)^+$

In vitro activity grade: B

^{1}H-NMR (300 MHz, DMSO-d6): d 7.53 - 7.62 (3 H , m), 7.70 (1H, t, J = 7.34 Hz), 8.00 (1H, d, J = 8.10 Hz), 8.30 (1H, d, J = 7.91 Hz), 8.44 (1H, s), 8.63 (1H, d, J = 7.72 Hz), 8.81 (1H, dd, J = 1.5, 4.7 Hz), 9.49 (1H, s), 13.49 (1H, br).

Example 4-2

N-Imidazo[1,2-*c*]quinazolin-5-ylnicotinamide hydrochloride



To a solution of *N*-imidazo[1,2-c]quinazolin-5-ylnicotinamide (40 mg, 0.14 mmol) in methanol (20 ml) was added a 4N solution of HCl in 1,4-dioxane (0.5 ml). The mixture was concentrated under reduced pressure. The resulting solid was collected by filtration, washed with tetrahydrofurane and dried under reduced pressure to give

N-imidazo[1,2-c]quinazolin-5-ylnicotinamide hydrochloride (40 mg, 89% yield) as a white solid.

Melting point: 228 °C (decomposition)

Molecular weight: 325.76

Mass spectrometry: 290 $(M + H)^+$

In vitro activity grade:

^{1}H-NMR (300 MHz, DMSO-d6): δ 7.60 (2H, br), 7.65 (1H, t, J = 7.5 Hz), 7.82 (1H, dd, J = 7.3, 8.1 Hz), 7.92 (1H, s), 8.02 (1H, dd, J = 5.5, 7.9 Hz), 8.54 (1H, d, J = 8.3 Hz), 8.73 (1H, s), 9.02 (1H, dd, J = 1.3, 5.3 Hz), 9.07 (1H, d, J = 7.53 Hz), 9.67 (1H, s).

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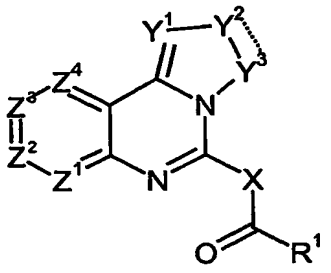
5

CLAIMS

1. An azole[1,2-c]quinazoline derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



wherein

X is NH, or CR^5R^6;

Y^1 is N or CR^3;

Y^2 and Y^3 are independently selected from the group consisting of CH, nitogen, CR^3R^4, or NR^4; the chemical bond between Y^2—Y^3 is selected from the group consisting of a single bond and double bond, Y^2 and Y^3 are the same or different represent CH or nitogen when the bond is a double, Y^2 and Y^3 are the same or different represent CR^3R^4 or NR^4 when the bond is a single;

Z^1, Z^2, Z^3 and Z^4 are the same or different represent N, CH, or CR^2;

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, C_{1-6} alkoxyaryl, aryloxy, or heteroaryl, C_{1-6} alkoxy optionally substituted by C_{1-6} alkyl, aryl, or one or more halogen, C_{1-6} alkylthio, N-arylamino, N(aryl C_{1-6}alkylene)amino, a 3 to 8 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of O, S, and N, and said ring is optionally having one or

more substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, amino, C_{1-6}alkyl optionally substituted by one or more halogen, C_{3-8}cycloalkyl, C_{1-6}alkoxy, carboxy, C_{1-6} alkylthio, C_{1-6}alkylsulfonyl, sulfamoyl, N- C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, heteroaryl optionally substituted by C_{1-6} alkyl or C_{1-6}alkoxy, heteroarylamino, heteroarylcarbonyl, heterocyclyl, hterocyclylcarbonyl, N-(C_{1-6}alkanoyl)amino, N(carboxyC_{1-6}-alkylene)N(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycabonyl)amino, and aryl C_{1-6}alkoxycarbonyl,

or

said a 3 to 8 membered saturated or unsaturated ring is optionally fused by a 5 to 8 membered unsaturated ring optionally interrupted by 0 to 3 heteroatoms selected from the group consisting of O, S, and N,

wherein said a fused ring is optionally substituted by C_{1-6}alkyl or one or more halogen substituted C_{1-6}alkyl;

R^2 is hydroxy, halogen, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by cyano one or more halogen, or amino, N-C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, or heterocyclyl;

R^3 is hydrogen, halogen, C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy or one or more halogen, or carbamoyl;

R^4 is hydrogen or C_{1-6} alkyl;

R^5 is hydrogen or C_{1-6} alkyl; and

R^6 is halogen, hydrogen, or C_{1-6} alkyl.

2. The azole[1,2-c]quinazoline derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, wherein

Z^1 and Z^3 are the same or different represent N or CH; and

Z^2 and Z^4 are the same or different represent CH or C R^2.

3. The azole[1,2-c]quinazoline derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

Z^1 and Z^3 are the same or different represent CH or C R^2;and

Z^2 and Z^4 are the same or different represent N or CH.

4. The azole[1,2-c]quinazoline derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

Z^1 and Z^4 are the same or different represent N or CH;

Z^2 and Z^3 are the same or different represent CH or CR^2;

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, methoxy-phenyl, phenoxy, or thienyl, C_{1-6} alkoxy optionally substituted by C_{1-6} alkyl, phenyl, or one or more halogen, C_{1-6} alkylthio, N-phenylamino,

N(phenyl C_{1-6}alkylene)amino, a 3 to 8 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of O, S, and N, and said ring is optionally having one or more substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, amino, C_{1-6}alkyl optionally substituted by one or more halogen, C_{1-6}alkoxy, carboxy, C_{1-6} alkylthio, C_{1-6}alkyl-sulfonyl, sulfamoyl, N- C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6}-alkoxy, C_{1-6}alkoxycarbonyl, piperazineyl optionally substituted by C_{1-6} alkyl or C_{1-6}alkoxy, N-(C_{1-6}alkanoyl)amino, N(carboxyC_{1-6} alkylene)N(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycarbonyl)amino, pyrrolyl, imidazolyl, pyrrolidinyl, pyridyl, and phenyl C_{1-6}alkoxycarbonyl,

or

said a 3 to 8 membered saturated or unsaturated ring is optionally fused by a 5 to 8 membered unsaturated ring optionally interrupted by 0 to 3 heteroatoms selected from the group consisting of O, S, and N,

wherein said a fused ring is optionally substituted by C_{1-6}alkyl or one or more halogen substituted C_{1-6}alkyl;

R^2 is hydroxy, halogen, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by cyano, one or more halogen, or amino, N-C_{1-6}-alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, or morpholinyl;

R^3 is halogen, hydrogen, C_{1-6} alkyl optionally substituted by arylC_{1-6} alkoxy, one or more halogen, or carbamoyl;

R^4 is hydrogen or C_{1-6} alkyl;

R^5 is hydrogen or C_{1-6} alkyl; and

R^6 is hydrogen, halogen, or C_{1-6} alkyl.

5. The azole[1,2-c]quinazoline derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

Z^1 and Z^4 are the same or different represent CH or CR^2;

Z^2 and Z^3 are the same or different represent N or CH;

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, methoxyphenyl, phenoxy, or thienyl, C_{1-6} alkoxy optionally substituted by C_{1-6} alkyl, phenyl, or one or more halogen, C_{1-6} alkylthio, N-phenylamino, N(phenyl C_{1-6}alkylene)amino, a 3 to 8 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of O, S, and N, and said ring is optionally having one or more substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, amino, C_{1-6}alkyl optionally substituted by mono, di, or tri, halogen, C_{1-6}alkoxy, carboxy, C_{1-6} alkylthio, C_{1-6}alkylsulfonyl, sulfamoyl, N- C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, piperazinly optionally substituted by C_{1-6} alkyl or C_{1-6}alkoxy, N-(C_{1-6}alkanoyl)amino, N(carboxyC_{1-6} alkylene)N(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycabonyl)amino, pyrrolyl, imidazolyl, pyrrolidinyl, pyridyl, and phenyl C_{1-6}alkoxycarbonyl,

or

said a 3 to 8 membered saturated or unsaturated ring is optionally fused by a 5 to 8 membered unsaturated ring optionally interrupted by 0 to 3 heteroatoms selected from the group consisting of O, S, and N,

wherein said a fused ring is optionally substituted by C_{1-6}alkyl or one or more halogen substituted C_{1-6}alkyl;

R^2 is hydroxy, halogen, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by cyano mono, di or tri halogen, or amino, N-C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, or morpholinyl;

R^3 is halogen, hydrogen, C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy or one or more halogen, or carbamoyl;

R^4 is hydrogen or C_{1-6} alkyl;

R^5 is hydrogen or C_{1-6} alkyl; and

R^6 is hydrogen, halogen, or C_{1-6} alkyl.

6. The azole[1,2-c]quinazoline derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, methoxyphenyl, phenoxy, or thienyl, C_{1-6} alkoxy optionally substituted by C_{1-6} alkyl, phenyl, or one or more halogen, C_{1-6} alkylthio, N-phenylamino, N(phenyl C_{1-6}alkylene)amino, a 3 to 8 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group

consisting of O, S, and N, and said ring is optionally having one or more substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, amino, C_{1-6}alkyl optionally substituted by mono, di, or tri, halogen, C_{1-6}alkoxy, carboxy, C_{1-6} alkylthio, C_{1-6}alkylsulfonyl, sulfamoyl, N- C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, piperazinly optionally substituted by C_{1-6} alkyl or C_{1-6}alkoxy, N-(C_{1-6}alkanoyl)amino, N(carboxyC_{1-6} alkylene)N(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycabonyl)amino, pyrrolyl, imidazolyl, pyrrolidinyl, pyridyl, and phenyl C_{1-6}alkoxycarbonyl,

or

said a 3 to 8 membered saturated or unsaturated ring is optionally fused by a 5 to 8 membered unsaturated ring optionally interrupted by 0 to 3 heteroatoms selected from the group consisting of O, S, and N, wherein said a fused ring is optionally substituted by C_{1-6}alkyl or mono, di, or tri halogen substituted C_{1-6}alkyl;

R^2 is hydroxy, halogen, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by cyano mono, di or tri halogen, or amino, N-C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, or morpholinyl;

R^3 is halogen, hydrogen, C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy, or one or more halogen, or carbamoyl;

R^4 is hydrogen or C_{1-6} alkyl; and

R^5 is hydrogen or C_{1-6} alkyl; and

R^6 is halogen, hydrogen or C_{1-6} alkyl.

7. The azole[1,2-c]quinazoline derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

Z^1 and Z^4 are CH;

Z^2 and Z^3 are the same or different represent CH or C R^2;

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, methoxyphenyl, phenoxy, or thienyl, C_{1-6} alkoxy optionally substituted by C_{1-6} alkyl, phenyl, or mono, di, or tri, halogen, C_{1-6} alkylthio, N-phenylamino, N(phenyl C_{1-6}alkylene)amino, a 3 to 8 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of O, S, and N,

wherein siad ring is selected from the group consisting of cyclopropyl, cyclopentyl, cyclohexyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, piperidinyl, piperazinyl, pyrimidyl, furyl, pyrrolidinyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, oxadiazolyl, and morpholinyl,

wherein said ring is optionally having 1 to 3 substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, amino, C_{1-6}alkyl optionally substituted by mono, di or tri halogen, C_{1-6}alkoxy, carboxy, C_{1-6} alkylthio, C_{1-6}alkylsulfonyl, sulfamoyl, N-(C_{1-6}alkyl)-amino, di(C_{1-6})alkylamino, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, piperazinyl optionally substituted by C_{1-6} alkyl or C_{1-6}alkoxy, N-(C_{1-6}alkylcabonyl)amino, N(carboxyC_{1-6} alkyl)N(C_{1-6}alkyl)amino, N-(C_{1-6}-

alkoxycabonyl)amino, imidazolyl, pyrrolyl, pyrrolidinyl, pyridyl, and phenyl C_{1-6}alkoxycabonyl,

or said a 3 to 8 membered saturated or unsaturated ring is optionally fused by a 5 to 8 membered unsaturated ring optionally interrupted by 0 to 3 heteroatoms selected from the group consisting of O, S, and N

wherein said fused ring is selected from the group consisting of benzothiophenly, benzimidazolyl, benzotriazolyl, benzothiazolyl, benzisothiazolyl indazolyl, quinolinly, and isoquinolinyl,

wherein said a fused ring is optionally substituted by C_{1-6}alkyl or mono, di, or tri halogen substituted C_{1-6}alkyl;

R^2 is chloro, bromo, fluoro, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by tri halogen, C_{1-6} alkoxy, or morpholinyl,

R^3 is halogen, hydrogen, C_{1-6} alkyl optionally substituted by aryl C_{1-6}-alkoxy or mono, di or tri halogen or carbamoyl;

R^4 is hydrogen, C_{1-6} alkyl or carbamoyl;

R^5 is hydrogen; and

R^6 is hydrogen.

8. The azole[1,2-c]quinazoline derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, wherein

X is NH;

Y^1 is N;

Y^2 and Y^3 are CR^3R^4;

Z^1 and Z^4 are CH;

Z^2 and Z^3 are the same or different represent CH or CR^2;

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, phenyl, C_{1-6}alkoxy substituted phenyl, phenoxy, or thienyl, cyclopropyl, cyclopentyl, cyclohexyl,

phenyl optionally substituted by halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, amino, N-(C_{1-6}-alkyl cabonyl)amino, N-(C_{1-6}alkoxycabonyl)amino, di(C_{1-6})alkyl-amino, N-(carboxyC_{1-6}alkylene)N-C_{1-6}alkyl amino, C_{1-6}alkanoyl-amino, C_{1-6} alkylthio, C_{1-6}alkylsulfonyl, sulfamoyl, piperazinyl optionally substituted by C_{1-6}alkyl, pyrrolyl, imidazolyl, pyrazolyl or pyrrolidinyl,

pyridyl optionally substituted by one or more halogen, hydroxy, C_{1-6}alkyl optinally substituted by mono, di or tri halogen, C_{1-6}alkoxy, C_{1-6}alkylthio, amino, di(C_{1-6})alkylamino, or C_{1-6}alkanoylamino, pyrazinyl optionally substituted by C_{1-6} alkyl,

2-thienyl optionally substituted by halogen, nitro, cyano, or C_{1-6} alkyl,

3-thienyl optionally substituted nitro, pyrimidinyl, pyridazinyl, or pyrrolyl optionally substituted by C_{1-6}alkyl,

piperidinyl optionally substituted by C_{1-6}alkoxycarbonyl, or benzyloxycarbonyl,

piperazinyl, pyrimidyl, 2-furyl, 3-furyl, isothiazolyl, thiadiazolyl,

thiazolyl optionally substituted by C_{1-6}alkyl, pyridyl, or N-(C_{1-6}alkoxycrbonyl)amino,

indolyl optionally substituted by C_{1-6}alkyl,

benzimidazolyl optionally substituted by C_{1-6}alkyl optionally substituted by mono, di or tri halogen,

benzotriazolyl optionally substituted by C_{1-6}alkyl, quinolyl benzthiazolyl, indole substituted by C_{1-6}alkyl, or bemzothhiophenyl

R^2 is hydroxy, halogen, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by cyano mono, di or tri halogen, or amino, N-C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, or morpholinyl;

R^3 is halogen, hydrogen, C_{1-6} alkyl or carbamoyl; and

R^4 is hydrogen or C_{1-6} alkyl.

9. The azole[1,2-c]quinazoline derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

X is CR^5R^6;

Y^1 is N;

Y^2 and Y^3 are C R^3 R^4;

Z^1 and Z^4 are CH;

Z^2 and Z^3 are the same or different represent CH or C R^2;

R^1 is C_{1-6} alkyl optionally substituted by one or more halogen, substituted phenyl, or phenoxy, C_{1-6}alkoxy optionally substituted by phenyl, benzylamino, cyclopropyl, cyclohexyl, phenyl optionally substituted by chloro, hydroxy, nitro, cyano, carboxyl, C_{1-6} alkyl, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, amino, di(C_{1-6})alkylamino, C_{1-6}alkanoylamino, C_{1-6} alkylthio, C_{1-6}alkylsulfonyl, or sulfamoyl, pyridyl optionally substituted by halogen, C_{1-6}alkyl, C_{1-6}alkoxy, pyrazinyl optionally substituted by C_{1-6} alkyl, 2-thienyl optionally substituted by halogen, cyano or nitro, 3-thienyl optionally substituted by halogen, cyano or nitro, pyrimidinyl, pyridazinyl, pyrrolyl, piperidinyl piperazinyl, pyrimidyl, furyl, thiazolyl optionally substituted by C_{1-6}alkyl, cyano, or C_{1-6}alkoxycarbonylamino, pyridyl, thiadiazolyl, and indolyl optionally substituted by C_{1-6}alkyl, or bemzothienyl; and

R^2 is chloro, bromo, nitro, amino, cyano, C_{1-6} alkyl optionally substituted by tri halogen, or C_{1-6} alkoxy;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is hydrogen; and

R^6 is hydrogen.

10. The azole[1,2-c]quinazoline derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, wherein said derivative is selected from the group consisting of the following compounds:

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-furamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophenecarboxamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3-thiophenecarboxamide,
3-amino-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,
4-amino-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
4-(acetylamino)-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-1,2,3-benzotriazole-5-carboxamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3,4-dimethoxybenzamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-6-methylnicotinamide,
2-chloro-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
6-chloro-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3-quinolinecarboxamide,
6-(acetylamino)-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methyl-1H-benzimidazole-5-carboxamide,
N-(9-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-thiophenecarboxamide,

N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophene-carboxamide,

N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotin-amide,

N-(10-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,

N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophene-carboxamide,

N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophene-carboxamide,

N-(9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophene-carboxamide,

(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-pyrazinyl)ethenol,

(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(4-pyridinyl)ethenol,

(1Z)-3,3,3-trichloro-1-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-propen-2-ol,

(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-furyl)ethenol,

(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-thienyl)ethenol,

(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(1H-pyrrol-2-yl)ethenol,

(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-thienyl)ethenol,

(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(1H-pyrrol-3-yl)ethenol,

(Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethenol,

(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(1,3-thiazol-2-yl)ethenol,

(Z)-2-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)-ethenol,

(Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-thienyl)ethenol,

N-{4-[(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxy-ethenyl]phenyl}acetamide,

(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(6-methyl-3-pyridinyl)-ethenol,

and
(Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(6-methyl-3-pyridinyl)ethenol.

11. A medicament comprising the azole[1,2-c]quinazoline derivative , its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

12. The medicament as claimed in claim 11, further comprising one or more pharmaceutically acceptable excipients.

13. The medicament as claimed in claim 11, wherein the azole[1,2-c]quinazoline derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is a PI3K-γ inhibitor.

14. An agent to treat or prevent a inflammatory or immunoregulatory disorder; comprising the azole[1,2-c]quinazoline derivative , its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

15. An agent to treat or prevent asthma, rhinitis, and allergic diseases, and autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis; comprising the azole[1,2-c]quinazoline derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

16. An agent to treat or prevent a neurodegenerative disorders, Alzheimer's disease, or focal ischemia; comprising the azole[1,2-c]quinazoline derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

17. An agent to treat a disease selected from the group consisting of ischemia, myocardial injury, pulmonary hypertension, renal failure, Huntington's chorea and cardiac hypertrophy; comprising the azole[1,2-c]quinazoline derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

18. A method for treating or preventing disorder or disease associated with PI3K-γ activity in a human or animal subject, comprising administering to said subject a therapeutically effective amount of the azole[1,2-c]quinazoline derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1.

19. The method of claim 18, wherein said disorder or disease is a inflammatory or immunoregulatory disorder or disease.

20. The method of claim 18, wherein said disorder or disease is selected from the group consisting of asthma, rhinitis, and allergic diseases, and autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis.

21. The method of claim 18, wherein said disorder or disease is selected from the group consisting of neurodegenerative disorders, Alzheimer's disease, focal ischemia, ischemia, myocardial injury, pulmonary hypertension, renal failure, Huntington's chorea and cardiac hypertrophy.

22. The method of claim 18, wherein said azole[1,2-c]quinazoline derivative is selected from the group consisting of:

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-furamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophenecarboxamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3-thiophenecarboxamide,
3-amino-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,
4-amino-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
4-(acetylamino)-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-1,2,3-benzotriazole-5-carboxamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3,4-dimethoxybenzamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-6-methylnicotinamide,
2-chloro-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
6-chloro-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3-quinolinecarboxamide,
6-(acetylamino)-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methyl-1H-benzimidazole-5-carboxamide,
N-(9-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-thiophenecarboxamide,
N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophene-carboxamide,
N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotin-amide,
N-(10-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophene-carboxamide,
N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophene-carboxamide,

N-(9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophene-carboxamide,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-pyrazinyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(4-pyridinyl)ethenol,
(1Z)-3,3,3-trichloro-1-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-propen-2-ol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-furyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-thienyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(1H-pyrrol-2-yl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-thienyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(1H-pyrrol-3-yl)ethenol,
(Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(1,3-thiazol-2-yl)ethenol,
(Z)-2-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)-ethenol,
(Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-thienyl)ethenol,
N-{4-[(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyethenyl]-phenyl}acetamide,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(6-methyl-3-pyridinyl)-ethenol,
and
(Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(6-methyl-3-pyridinyl)ethenol.

23. The method of claim 18, wherein said azole[1,2-c]quinazoline derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is administered with one or more pharmaceutically acceptable excipients.

24. Use of the azole[1,2-c]quinazoline derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 in the preparation of a medicament.

25. Use of azole[1,2-c]quinazoline derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 in the preparation of a medicament for treating or preventing disorder or disease associated with PI3K-γ activity.

26. The use of claim 25, wherein said disorder or disease is a inflammatory or immunoregulatory disorder or disease.

27. The use of claim 25, wherein said disorder or disease is selected from the group consisting of asthma, rhinitis, and allergic diseases, and autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis.

28. The use of claim 25, wherein said disorder or disease is selected from the group consisting of neurodegenerative disorders, Alzheimer's disease, focal ischemia, ischemia, myocardial injury, pulmonary hypertension, renal failure, Huntington's chorea and cardiac hypertrophy.

29. The use of claim 25, wherein said azole[1,2-c]quinazoline derivative is selected from the group consisting of:

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-furamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophenecarboxamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3-thiophenecarboxamide,
3-amino-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,
4-amino-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
4-(acetylamino)-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)benzamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-1,2,3-benzotriazole-5-carboxamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3,4-dimethoxybenzamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-6-methylnicotinamide,
2-chloro-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
6-chloro-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3-quinolinecarboxamide,
6-(acetylamino)-N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methyl-1H-benzimidazole-5-carboxamide,
N-(9-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-thiophenecarboxamide,
N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophenecarboxamide,
N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide,
N-(10-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide,
N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophenecarboxamide,
N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophenecarboxamide,
N-(9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-thiophenecarboxamide,

(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-pyrazinyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(4-pyridinyl)ethenol,
(1Z)-3,3,3-trichloro-1-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-propen-2-ol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-furyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-thienyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(1H-pyrrol-2-yl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-thienyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(1H-pyrrol-3-yl)ethenol,
(Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethenol,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(1,3-thiazol-2-yl)ethenol,
(Z)-2-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)-ethenol,
(Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2-thienyl)ethenol,
N-{4-[(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyethenyl]-phenyl}acetamide,
(Z)-2-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(6-methyl-3-pyridinyl)-ethenol,
and
(Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(6-methyl-3-pyridinyl)ethenol.

30. The use of claim 25, wherein said azole[1,2-c]quinazoline derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is formulated with one or more pharmaceutically acceptable excipients.

AZOLE [1,2-C]QUINAZOLINE DERIVATIVES

ABSTRACT

The present invention relates to novel azole[1,2-c]quinazoline derivatives, processes for preparing them and pharmaceutical preparations containing them. The azole[1,2-c]quinazoline derivatives of the present invention exhibit enhanced potency for phosphotidylinositol-3-kinase-γ (PI3K-γ) inhibition and can be used for the prophylaxis and treatment of diseases associated with PI3K-γ activity.

More specifically, the azole[1,2-c]quinazoline derivatives of the present invention are useful for treatment and prophylaxis of diseases as follows: inflammatory and immunoregulatory disorders, such as asthma, atopic dermatitis, rhinitis, allergic rhinitis, allergic diseases, COPD, septic shock, arthritis, joint diseases and myocardial injuries, as well as autoimmune pathologies such as rheumatoid arthritis, Grave's disease, and atherosclerosis.

The compounds of the present invention are also useful for treatment of ischemia, myocardial injury, pulmonary hypertension, renal failure, Huntington's chorea and cardiac hypertrophy, as well as neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease and focal ischemia, since the diseases also relate to PI3K-γ.